

# PATENT SPECIFICATION

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## (54) CEPHALOSPORIN DERIVATIVES

(71) We, GLAXO LABORATORIES LIMITED, a British Company, of Greenford, Middlesex, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention is concerned with improvements in or relating to cephalosporin compounds, and is more particularly concerned with a novel class of cephalosporin compounds possessing valuable antibiotic properties.

The cephalosporin compounds in this specification are named with reference to "cepham" after *J. Amer. Chem. Soc.*, 1962, 84, 3400, the term "cepham" referring to the basic cepham structure with one double bond.

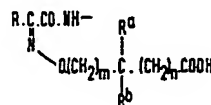
Cephalosporin antibiotics are widely used in the treatment of diseases caused by pathogenic bacteria in human beings and animals, for example in the treatment of diseases caused by bacteria which are resistant to other antibiotics such as penicillin compounds, and in the treatment of penicillin-sensitive patients.

In many instances it is desirable to employ a cephalosporin antibiotic which exhibits activity against both gram positive and gram negative microorganisms, and a significant amount of research has been directed to the development of various types of broad spectrum cephalosporin antibiotics.

Considerable interest is currently being directed to the development of broad spectrum cephalosporin antibiotics which possess high activity against gram negative organisms. Existing commercially available  $\beta$ -lactam antibiotics tend to exhibit comparatively low

activity against certain gram negative organisms such as *Proteus* organisms, which are an increasingly common source of infection in humans, and are also generally substantially inactive against *Pseudomonas* organisms. Several *Pseudomonas* organisms are resistant to the majority of existing commercially available antibiotic compounds, and the practical therapeutic applications of aminoglycoside antibiotics such as gentamicin which do exhibit *Pseudomonas* activity tend to be limited or complicated by the high toxicity of these antibiotics. It is well known that cephalosporin antibiotics normally exhibit low toxicity in man, so that the development of broad spectrum cephalosporin antibiotics possessing high activity against gram negative organisms such as strains of *Proteus* and *Pseudomonas* fulfils a significant need in chemotherapy.

The present invention provides  $7\beta$ -acylamidoceph-3-em-4-carboxylic acid antibiotics and non-toxic derivatives thereof which are characterised in that the said acylamido moiety has the formula



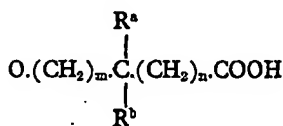
[wherein R is a thienyl or furyl group; R<sup>a</sup> and R<sup>b</sup>, which may be the same or different, are each selected from hydrogen, C<sub>1-4</sub> alkyl (e.g. methyl, ethyl, n-propyl, isopropyl or butyl), C<sub>2-4</sub> alkenyl (e.g. vinyl or allyl), C<sub>3-7</sub> cycloalkyl (e.g. cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl), phenyl, naphthyl,

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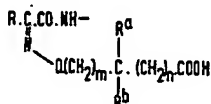
thienyl, furyl, carboxy, C<sub>2-8</sub> alkoxy-carbonyl (e.g. ethoxycarbonyl) and cyano, or R<sup>a</sup> and R<sup>b</sup> together with the carbon atom to which they are attached form a C<sub>2-7</sub> cycloalkylidene or cycloalkenylidene group (e.g. a cyclobutylidene, cyclopentylidene or cyclohexylidene group); and *m* and *n* are each 0 or 1, such that the sum of *m* and *n* is 0 or 1, the compounds being *syn* isomers or existing as mixtures of *syn* and *anti* isomers containing at least 90% of the *syn* isomer.

These compounds exhibit broad spectrum antibiotic activity characterised by particularly high activity against gram negative micro-organisms, including those which produce β-lactamases, and also possess very high stability to β-lactamases produced by a range of gram negative organisms. A characteristic feature of the compounds is their high *in vitro* activity against gram-negative organisms such as *Enterobacter cloacae*, *Serratia marcescens* and *Klebsiella aerogenes*. The compounds have particularly high activity against strains of *Escherichia coli*, *Haemophilus influenzae* and *Proteus* organisms, e.g. strains of *Proteus morganii* and *Proteus mirabilis*. Compounds wherein at least one of R<sup>a</sup> and R<sup>b</sup> is other than hydrogen have also shown unusually high activity against *Pseudomonas* organisms, for example strains of *Pseudomonas aeruginosa* for example strains of *Pseudomonas aeruginosa*.

The compounds of the invention are defined as having the *syn* isomeric form as regards the configuration of the group.

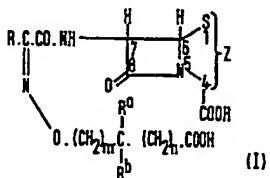


with respect to the carboxamido group. In this specification the *syn* configuration is denoted structurally as



this configuration being assigned on the basis of the work of Ahmed and Spenser in *Can. J. Chem.*, 1961, 39, 1340. As indicated above, the compounds may exist as mixtures of *syn* and *anti* isomers provided that such mixtures contain at least 90% of the *syn* isomer. We prefer, however, the compounds to be *syn* isomers essentially free from the corresponding *anti* isomer.

The antibiotic compounds of the invention therefore comprise compounds of the general formula:



(wherein R, R<sup>a</sup>, R<sup>b</sup>, *m* and *n* have the above-defined meanings and Z is a group in which 2 carbon atoms link the nuclear sulphur atom and the 4-position carbon atom such that the compound possesses Δ<sup>3</sup> olefinic unsaturation) and non-toxic derivatives thereof.

By "non-toxic derivatives" is meant those derivatives which are physiologically acceptable in the dosage at which they are administered. Such derivatives may include, for example, salts, biologically acceptable esters, 1-oxides and solvates (especially hydrates). It will be appreciated that derivatives such as salts and esters may be formed by reaction of either or both of the carboxyl groups present in the compounds of formula I.

Non-toxic salt derivatives which may be formed from the compounds of general formula I include inorganic base salts such as alkali metal salts (e.g. sodium and potassium salts) and alkaline earth metal salts (e.g. calcium salts); organic base salts (e.g. procaine, phenylethylbenzylamine, dibenzylethylenediamine, ethanolamine, diethanolamine, triethanolamine and N-methylglucosamine salts); and, where appropriate, acid addition salts, e.g. with hydrochloric, hydrobromic, sulphuric, nitric, phosphoric, trifluoroacetic, toluene -*p*-sulphonic and methane sulphonic acids. The salts may also be in the form of resinsates formed with, for example, a polystyrene resin or cross-linked polystyrene divinylbenzene copolymer resin containing amino or quaternary amino groups, or, where appropriate, sulphonic acid groups, or, again where appropriate, with a resin containing carboxyl groups, e.g. a polyacrylic acid resin. Use of highly soluble base salts (e.g. alkali metal salts such as the sodium salt) of compounds of formula I is generally advantageous in therapeutic applications because of the rapid distribution of such salts in the body upon administration. Where, however, insoluble salts of compounds (I) are desired in a particular application, e.g. for use in depot preparations, such salts may be formed in conventional manner, for example with appropriate organic amines.

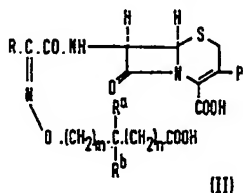
Biologically acceptable, metabolically labile ester derivatives which may be formed from compounds of formula I include, for example, acyloxymethyl esters, e.g. lower alkanoyloxymethyl esters such as acetoxy-methyl or pivaloyloxymethyl esters.

Where the group R in the above formulae is a furyl group it may be fur - 2 - yl or

fur - 3 - yl and where it is a thienyl group it may be thien - 2 - yl or thien - 3 - yl.

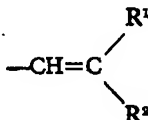
It will be appreciated that when  $R^a$  and  $R^b$  in the above formulae are different, the carbon atom to which they are attached may comprise a centre of asymmetry; compounds in accordance with the invention wherein  $R^a$  and  $R^b$  are different may thus be diastereoisomeric. The invention embraces the individual diastereoisomers of such compounds as well as mixtures thereof.

The cephalosporin antibiotics according to the present invention may be unsubstituted at the 3-position or may carry at this position any of the wide range of substituents disclosed in the literature pertaining to cephalosporin compounds, the characterising feature of the invention being the nature of the 7 $\beta$ -acylamido group. The invention thus includes within its scope compounds of the general formula:



[where  $R$ ,  $R^a$ ,  $R^b$ ,  $m$  and  $n$  are as hereinbefore defined and  $P$  represents a hydrogen atom; a halogen atom such as fluorine, chlorine or bromine; or an organic group, for example a saturated or unsaturated, substituted or unsubstituted, organic group containing 1-20 carbon atoms] and non-toxic derivatives thereof.

Where  $P$  is an unsaturated organic group it may, for example, be a group of the formula



wherein  $R^1$  and  $R^2$ , which may be the same or different, are each selected from hydrogen, carboxy, cyano,  $C_{2-7}$  alkoxy carbonyl (e.g. methoxycarbonyl or ethoxycarbonyl), and substituted or unsubstituted aliphatic (e.g. alkyl, preferably  $C_1-C_4$  alkyl such as methyl, ethyl, iso-propyl or n-propyl),  $C_6-C_7$  cycloaliphatic (e.g.  $C_5-C_7$  cycloalkyl such as cyclopentyl or cyclohexyl),  $C_1-C_{10}$  araliphatic (e.g. phenyl  $C_1-C_{12}$  alkyl such as benzyl or phenylethyl) and  $C_6-C_{12}$  aromatic (e.g. mono- or bicyclic carbocyclic aryl such as phenyl, nitrophenyl, tolyl or naphthyl) groups. Specific substituted vinyl groups of the above formula include 2-carboxyvinyl, 2-methoxycarbonylvinyl, 2-ethoxycarbonylvinyl and 2-cyanovinyl.

$P$  may also be a substituted methyl group, which may be depicted by the formula



where  $Y$  is an atom or group, e.g. the residue of a nucleophile or a derivative of a residue of a nucleophile.  $Y$  may thus, for example, be derived from the wide range of nucleophilic substances characterised by possessing a nucleophilic nitrogen, carbon, sulphur or oxygen atom described widely in earlier patents and literature pertaining to cephalosporin chemistry. Examples of such nucleophiles include:—

#### NITROGEN NUCLEOPHILES

Examples of nitrogen nucleophiles include tertiary aliphatic, aromatic, araliphatic and cyclic amines, for example tri( $C_{1-4}$  alkyl) amines such as triethylamine, and heterocyclic tertiary amines. The heterocyclic tertiary amines may if desired contain one or more further heteroatoms in addition to the basic nitrogen atom, and may be substituted or unsubstituted. The heterocyclic tertiary amine may thus, for example, be pyridine, pyrimidine, pyridazine, pyrazine, pyrazole, imidazole, triazole or thiazole; a fused bi- or polycyclic analogue of any of these heterocycles, for example purine or benzotriazole; and any of the above amines substituted by one or more aliphatic (e.g. lower alkyl such as methyl, ethyl, n-propyl or isopropyl), aryl (e.g.  $C_{6-12}$  mono- or bicyclic carbocyclic aryl such as phenyl or naphthyl), araliphatic (e.g. phenyl lower alkyl such as benzyl or phenylethyl), lower alkoxy methyl (e.g. methoxymethyl, ethoxymethyl, n-propoxymethyl or isopropoxymethyl) acyloxymethyl (e.g. lower alkanoyloxymethyl such as acetoxymethyl), formyl, acyloxy (e.g. lower alkanoyloxy such as acetoxymethyl), carboxy, esterified carboxy (e.g. lower alkoxy carbonyl such as methoxycarbonyl), carboxy lower alkyl (e.g. carboxymethyl), sulphonyl, lower alkoxy (e.g. methoxy, ethoxy, n-propoxy or iso-propoxy), aryloxy (e.g. phenoxy), aralkoxy (e.g. benzyloxy), alkylthio, (e.g. methylthio or ethylthio), arylthio, aralkylthio, cyano, hydroxy, carbamoyl, N-monolower-alkylcarbamoyl (e.g. N-methylcarbamoyl or N-ethylcarbamoyl), N,N-diloweralkylcarbamoyl (e.g. N,N-dimethylcarbamoyl or N,N-diethylcarbamoyl), N - (hydroxylower-alkyl)carbamoyl (e.g. N - (hydroxymethyl)carbamoyl or N - (hydroxyethyl)carbamoyl), or carbamoyl lower alkyl (e.g. carbamoylmethyl or carbamoylethyl) groups. Examples of  $Y$  groups which may be obtained from heterocyclic tertiary amine nucleophiles of the above type include pyridinium, 3- and 4-carbamoylpyridinium, 3-carboxymethylpyridinium, 3-sulphopyridinium, thiazol - 3 - yl, pyrazol - 1 - yl, pyridazininium, and benzotriazol - 1 - yl.

Another class of nitrogen nucleophiles comprises azides, e.g. alkali metal azides such as sodium azide.

When the group Y is a derivative of a residue of a nitrogen nucleophile it may be, for example, an amino group or an acylamido group. Compounds in which Y is amino may be derived from the corresponding compound in which Y is azido by reduction, e.g. by catalytic hydrogenation of the azide using a precious metal catalyst such as palladium or platinum. Compounds in which Y is an acylamido group may be derived by acylation of a compound wherein Y is amino, e.g. by any method suitable for acylating an aminocephalosporin, for example reaction of the amino compound with an acid chloride, acid anhydride or mixed anhydride of an acid corresponding to the desired acyl group and another acid.

Compounds wherein Y is amino may also be reacted with a substituted isocyanate or isothiocyanate to yield urea or thiourea derivatives.

Other compounds in which Y is a derivative of a residue of a nitrogen nucleophile may be obtained by reacting a compound in which Y is azido with a dipolarophile. Examples of suitable dipolarophiles include acetylenic, ethylenic and cyano dipolarophiles.

Acetylenic dipolarophiles may be shown as having the structure



wherein R<sup>3</sup> and R<sup>4</sup>, which may be the same or different, are atoms or groups.

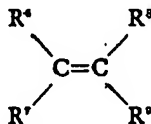
In general we prefer that R<sup>3</sup> and preferably also R<sup>4</sup> should be of an electronegative nature. Examples of such groups include cyano, CO<sub>2</sub>R<sup>5</sup>, COR<sup>5</sup> (where R<sup>5</sup> is, for example, hydrogen, lower alkyl, aryl or lower aralkyl), and trihalomethyl e.g. trifluoromethyl.

However, R<sup>3</sup> and preferably also R<sup>4</sup> could be electropositive e.g. alkoxy or alkylamino.

R<sup>3</sup> and R<sup>4</sup> may together form a ring system with the acetylenic group such as, for example, in an aryne.

Where R<sup>3</sup> and R<sup>4</sup> are discrete atoms or groups which are identical a single compound will result on reaction with the azido cephalosporin; if they are different one will in general obtain a mixture of position isomers.

Ethylenic dipolarophiles may be shown as having the structure



where R<sup>6</sup>, R<sup>7</sup>, R<sup>8</sup> and R<sup>9</sup> which may be the same or different are atoms or groups. Although R<sup>6</sup>, R<sup>7</sup>, R<sup>8</sup> and R<sup>9</sup> may all be hydrogen, ethylene *per se*, like acetylene, reacts sluggishly with azido groups. R<sup>6</sup> and R<sup>8</sup> may together form a cyclic structure, e.g. a carbo-

cyclic structure, with the ethenoid group such that the double bond is strained. Examples of ethylenic dipolarophiles containing strained double bonds include norbornenes, transcycloalkenes and acenaphthalene.

Further ethylenic dipolarophiles which may be used include compounds of the formula R<sup>6</sup> · R<sup>7</sup>C=CR<sup>8</sup> · R<sup>9</sup> where at least one of R<sup>6</sup>, R<sup>7</sup>, R<sup>8</sup> and R<sup>9</sup> is an electronegative group. R<sup>6</sup> and R<sup>8</sup> may thus be identical electronegative groups, R<sup>7</sup> and R<sup>9</sup> being other groups as desired. R<sup>7</sup> and R<sup>9</sup> may thus together form a ring system. Examples of such dipolarophiles include benzoquinone and nuclear substituted benzoquinones and maleimide. Again all of R<sup>6</sup>, R<sup>7</sup>, R<sup>8</sup> and R<sup>9</sup> may be identical electronegative groups. Electronegative groups which may be used include those listed under the section on acetylenic dipolarophiles and examples of such compounds thus include dicyanoethylene and lower mono- and di-alkoxycarbonyl ethylenes.

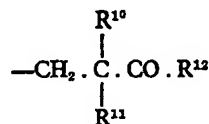
One or more of R<sup>6</sup>, R<sup>7</sup>, R<sup>8</sup> and R<sup>9</sup> may if desired be electropositive.

Cyano compounds, especially those which are activated by electronegative groups, may function as cyano dipolarophiles. Examples of such compounds include lower alkoxy-carbonyl cyanides and cyanogen.

#### CARBON NUCLEOPHILES

Examples of carbon nucleophiles include inorganic cyanides, pyrroles and substituted pyrroles, e.g. indoles, and compounds giving stabilised carbanions, for example acetylenes and compounds having β-diketone groups, for example acetoacetic and malonic esters and cyclohexane - 1,3 - diones or enamines, ynamines or enols.

The carbon nucleophile may thus give rise to cephalosporin compounds characterised by possessing a substituent at the 3-position in which a carbonyl group is linked to the cephalosporin nucleus through two carbon atoms. Such compounds may thus possess as the 3-substituent a group of the formula



wherein R<sup>10</sup> and R<sup>11</sup>, which may be the same or different, are selected from hydrogen; cyano; lower alkyl e.g. methyl or ethyl; phenyl; phenyl substituted by, for example, halo, lower alkyl, lower alkoxy, nitro, amino or lower alkylamino; carboxy; lower alkoxy-carbonyl; mono- or di-aryl lower alkoxy-carbonyl; lower alkylcarbonyl; aryl lower alkyl or C<sub>6</sub> or C<sub>5</sub> cycloalkyl and R<sup>12</sup> is selected from hydrogen; lower alkyl e.g. methyl or ethyl; phenyl; phenyl substituted by, for example, halo, lower alkyl, lower alkoxy, nitro,

amino or lower alkylamino; aryl lower alkyl or C<sub>6</sub> or C<sub>4</sub> cycloalkyl.

### SULPHUR NUCLEOPHILES

5 Examples of sulphur nucleophiles include thioureas, including aliphatic, aromatic, araliphatic, alicyclic and heterocyclic substituted thioureas; dithiocarbamates; aromatic, aliphatic and cyclic thioamides, for example thioacetamide and thiosemicarbazide; thio-  
10 sulphates; thiols; thiophenols; thioacids, e.g. thiobenzoic acid or thiopicolinic acid; and dithioacids.

One class of sulphur nucleophile includes those compounds of the formula:



in which R<sup>13</sup> is an aliphatic e.g. lower alkyl such as methyl, ethyl or n-propyl group; an alicyclic e.g. lower cycloalkyl such as cyclohexyl or cyclopentyl group; an aromatic e.g. C<sub>6-12</sub> mono- or bicyclic carbocyclic aryl such as phenyl or naphthyl group; an araliphatic e.g. phenyl lower (e.g. C<sub>1-4</sub>) alkyl such as benzyl group; or a heterocyclic group, and *n* is 0, 1 or 2. A preferred class of nucleophiles falling within the above formula is that having the general formula R<sup>14</sup> SH in which R<sup>14</sup> is aliphatic, e.g. lower alkyl such as methyl, ethyl or n-propyl or lower alkanoyl such as acetyl; araliphatic, e.g. phenyl lower alkyl such as benzyl or phenethyl or substituted phenyl lower alkyl; alicyclic, e.g. cycloalkyl such as cyclopentyl or cyclohexyl; aromatic, e.g. phenyl, substituted phenyl or a heterocyclic group containing at least one 5- or 6-membered ring and having one or more heteroatoms selected from O, N and S. Such heterocyclic groups R<sup>14</sup> may be substituted, and examples of suitable heterocyclic groups include thiadiazolyl, e.g. 5 - methyl - 1,3,4 - thiadiazol - 2 - yl; diazolyl; triazolyl, e.g. triazol - 4 - yl; tetrazolyl, e.g. 1 - methyl-tetrazol - 5 - yl, 1 - ethyltetrazol - 5 - yl or 1 - phenyltetrazol - 5 - yl; thiazolyl; thiatriazolyl; oxazolyl; oxadiazolyl, e.g. 2 - phenyl - 1,3,4 - oxadiazol - 5 - yl; pyridyl, e.g. N - methylpyrid - 2 - yl; pyrimidyl; fused heterocyclic ring systems such as benzimidazolyl; benzoxazolyl, benzothiazolyl such as benzothiazol - 2 - yl, triazolopyridyl or purinyl; and substituted versions of such fused ring systems, e.g. nitrobenzothiazol - 2 - yl such as 5- or 6 - nitrobenzothiazol - 2 - yl.

### OXYGEN NUCLEOPHILES

55 Examples of oxygen nucleophiles include water; alcohols, for example alkanols such as methanol, ethanol, propanol and butanol; and lower alkanolic and alkenoic acids.

60 The term "oxygen nucleophile" thus includes compounds of the following formula:



in which the group R<sup>15</sup> may be lower alkyl (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl or isobutyl); lower alkenyl (e.g. allyl); lower alkynyl (e.g. propynyl); lower cycloalkyl (e.g. cyclopropyl, cyclopentyl or cyclohexyl); lower cycloalkyl lower alkyl (e.g. cyclopropylmethyl, cyclopentylmethyl or cyclohexylethyl); aryl (e.g. phenyl or naphthyl); aryl lower alkyl (e.g. benzyl); heterocyclic (e.g. a heterocyclic group as defined for R<sup>14</sup>, such as N - methylpyrid - 2 - yl); heterocyclic lower alkyl (e.g. furfuryl); or any of these groups substituted by, for example, one or more of lower alkoxy (e.g. methoxy or ethoxy), lower alkylthio (e.g. methylthio or ethylthio), halogen (chlorine, bromine, iodine or fluorine), lower alkyl (e.g. methyl or ethyl), nitro, hydroxy, acyloxy, carboxy, carbalkoxy, lower alkylcarbonyl, lower alkylsulphonyl, lower alkoxy sulphonyl, amino, lower alkylamino or acylamino groups.

In the case in which water is the nucleophile there will be obtained 3-hydroxymethyl cephalosporin compounds. Such 3-hydroxymethyl compounds and non-toxic derivatives thereof may show antibacterial activity and it is of note that they may be metabolites of compounds of general formula II where P is acetoxymethyl. 3-Hydroxymethyl cephalosporins may be acylated to form derivatives characterized by possessing the group 3—CH<sub>2</sub>.O.CO.R<sup>16</sup> or 3—CH<sub>2</sub>.O.CO.AR<sup>17</sup> where A is O, S or NH, R<sup>16</sup> is an organic group and R<sup>17</sup> is hydrogen or an organic group.

The group R<sup>16</sup>CO— or R<sup>17</sup>A.CO— may be chosen from among the wide class of such groups described in the literature and may have up to 20 carbon atoms. R<sup>16</sup> and, where appropriate, R<sup>17</sup> may thus each be a hydrocarbon group or such a group carrying one or more substituent atoms or groups, and may thus be chosen from the following list, which is not intended to be exhaustive:—

(i) C<sub>n</sub>H<sub>2n+1</sub> where *n* is an integer from 1 to 7, e.g. 1 to 4. The group may be straight or branched and, if desired, may be interrupted by an oxygen or sulphur atom or an imino group or substituted by cyano, carboxy, lower alkoxy carbonyl, hydroxy, carboxy carbonyl (HOOC.CO), halogen (e.g. chlorine, bromine or iodine) or amino. Examples of such groups include methyl, ethyl, propyl, isopropyl, n-butyl, t-butyl, sec.butyl and 2-chloroethyl.

(ii) C<sub>n</sub>H<sub>2n-1</sub> where *n* is an integer from 2 to 7. The group may be straight or branched and, if desired, may be interrupted by an oxygen or sulphur atom or an imino group. Examples of such groups include vinyl and propenyl.

(iii) R<sup>18</sup>, where R<sup>18</sup> is carbocyclic aryl (e.g. C<sub>6-12</sub> mono- or bicyclic carbocyclic aryl),

heterocyclic aryl (e.g. comprising a 5- or 6-membered ring containing at least one of O, N and S), lower cycloalkyl, substituted aryl and substituted cycloalkyl. Examples of this group include phenyl; substituted phenyl e.g. hydroxyphenyl, chlorophenyl, fluorophenyl, tolyl, nitrophenyl, aminophenyl, methoxyphenyl or methylthiophenyl; thien - 2 - and - 3 - yl; pyridyl; cyclohexyl; cyclopentyl; cyclopropyl; sydnonyl; naphthyl; and substituted naphthyl e.g. 2-ethoxynaphthyl.

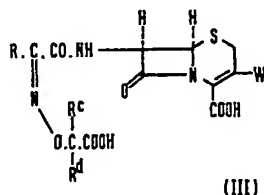
(iv)  $R^{18} (CH_2)_m$  where  $R^{18}$  has the meaning defined above under (iii) and  $m$  is an integer from 1 to 4. Examples of this group include methyl, ethyl or butyl substituted by the various specific  $R^{18}$  groups listed under (iii), e.g. lower cycloalkyl  $C_{1-4}$  alkyl and carbocyclic or heterocyclic aryl  $C_{1-4}$  alkyl such as benzyl and the appropriate substituted benzyl groups.

3-Position substituents of the above type thus include lower alkanoyloxymethyl groups such as acetoxymethyl and isobutyryloxymethyl, lower alkenoyloxymethyl groups such as crotonyloxymethyl; aroyloxymethyl groups such as benzoyloxymethyl; carbamoyloxymethyl, N - (lower alkyl)carbamoyloxymethyl such as N - methylcarbamoyloxymethyl, and N - (haloalkyl)carbamoyloxymethyl such as N - (2 - chloroethyl)carbamoyloxymethyl.

A further important class of cephalosporin compounds are those possessing the group  $3-CH_2Hal$  wherein Hal is chlorine, bromine or iodine. Such compounds may be primarily of value as intermediates of use in the preparation of active cephalosporin compounds by replacement of the halogen atom by a nucleophile e.g. a nitrogen-, oxygen- or sulphur-containing nucleophile as hereinbefore described.

The term "lower" as used in this specification and the accompanying claims to qualify aliphatic groups denotes, unless otherwise stated, that the said group may contain up to 6 carbon atoms. "Lower" as used to qualify cycloaliphatic groups indicated that the group may contain 3-7 (e.g. 5-7) carbon atoms.

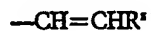
A particularly interesting class of cephalosporin antibiotics in accordance with the invention comprises compounds of general formula



[wherein R is as hereinbefore defined,  $R^c$  represents methyl, ethyl, propyl, allyl or phenyl and  $R^d$  represents hydrogen, carboxy or, more preferably, a group as defined for  $R^c$ ; or  $R^c$  and  $R^d$  together with the carbon

atom to which they are attached form a cyclobutylidene, cyclopentylidene or cyclohexylidene group; and W is selected from:—

- i) hydrogen,
- ii) acetoxymethyl,
- iii) benzoyloxymethyl,
- iv) carbamoyloxymethyl,
- v) N-methylcarbamoyloxymethyl,
- vi) a group of formula



(where  $R^*$  represents cyano, carboxy or a  $C_{2-6}$  alkoxy-carbonyl group such as methoxy-carbonyl or ethoxy-carbonyl),

vii) the group  $-CH_2G$  where G is the residue of a nitrogen nucleophile selected from compounds of the formula



(wherein  $R^f$  is hydrogen, carbamoyl, carboxy-methyl or sulphy) and pyridazine,

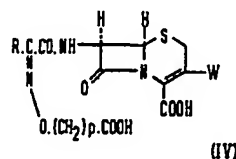
- viii) azidomethyl, and
- ix) the group  $-CH_2SR^w$  wherein  $R^w$  is selected from pyridyl, diazoly, triazolyl, tetrazolyl, thiazolyl, thiadiazolyl, oxadiazolyl, and substituted (e.g. lower alkyl- or phenyl-substituted) versions of these groups such as N - methylpyrid - 2 - yl, 1 - methyltetrazol - 5 - yl, 1 - phenyltetrazol - 5 - yl; 5 - methyl - 1,3,4 - thiadiazol - 2 - yl and 5 - phenyl - 1,3,4 - oxadiazol - 2 - yl] and non-toxic derivatives thereof.

These compounds exhibit broad spectrum antibiotic activity (including very high activity against strains of *Haemophilus influenzae* and *Proteus* organisms) and high  $\beta$ -lactamase stability and are further characterised by particularly high *in vitro* activity against *Pseudomonas* organisms such as strains of *Pseudomonas aeruginosa*.

Especially preferred compounds of the above type, by virtue of their particularly high levels of activity against *Proteus* and *Pseudomonas* organisms, include the following:—

- (6R,7R) - 7 - [2 - (2 - carboxyprop - 2 - yloxyimino) - 2 - (fur - 2 - yl) acetamido] - 3 - pyridiniummethylceph - 3 - em - 4 - carboxylic acid (*syn* isomer),
- (6R,7R) - 7 - [2 - (2 - carboxyprop - 2 - yloxyimino) - 2 - (fur - 2 - yl) acetamido] - 3 - (5 - methyl - 1,3,4 - thiadiazol - 2 - ylthiomethyl)ceph - 3 - em - 4 - carboxylic acid (*syn* isomer),
- (6R,7R) - 7 - [2 - (2 - carboxyprop - 2 - yloxyimino) - 2 - (fur - 2 - yl)acetamido] - 3 - (*trans* - 2 - methoxycarbonylvinyl)ceph - 3 - em - 4 - carboxylic acid (*syn* isomer),
- (6R,7R) - 7 - [2 - (2 - carboxyprop - 2 - yloxyimino) - 2 - (fur - 2 - yl) acet-

- amido] - 3 - pyridiniummethylceph - 3 -  
em - 4 - carboxylic acid (*syn* isomer),  
(6R,7R) - 7 - [2 - (2 - carboxyprop - 2 -  
yloxyimino) - 2 - (fur - 2 - yl) acet-  
amido]ceph - 3 - em - 4 - carboxylic acid  
5 (*syn* isomer),  
(6R,7R) - 3 - acetoxymethyl - 7 - [2 - (1 -  
carboxycyclopent - 1 - yloxyimino) - 2 -  
(fur - 2 - yl)acetamido]ceph - 3 - em - 4 -  
10 carboxylic acid (*syn* isomer),  
(6R,7R) - 7 - [2 - (1 - carboxycyclopent -  
1 - yloxyimino) - 2 - (fur - 2 - yl) acet-  
amido] - 3 - pyridiniummethylceph - 3 -  
em - 4 - carboxylic acid (*syn* isomer),  
15 (6R,7R) - 7 - [2 - (1 - carboxycyclopent -  
1 - yloxyimino) - 2 - (fur - 2 - yl) acet-  
amido] - 3 - (*trans* - 2 - carboxyvinyl)-  
ceph - 3 - em - 4 - carboxylic acid (*syn*  
isomer),  
20 (6R,7R) - 7 - [2 - (1 - carboxycyclopent -  
1 - yloxyimino) - 2 - (fur - 2 - yl)acet-  
amido] - 3 - (1 - methyltetrazol - 5 -  
ylthiomethyl)ceph - 3 - em - 4 - carboxylic  
acid (*syn* isomer),  
25 (6R,7R) - 7 - [2 - (1 - carboxycyclopent -  
1 - yloxyimino) - 2 - (fur - 2 - yl)acet-  
amido]ceph - 3 - em - 4 - carboxylic  
acid (*syn* isomer),  
30 (6R,7R) - 3 - acetoxymethyl - 7 - [2 - (1 -  
carboxybut - 3 - enyloxyimino) - 2 - (fur -  
2 - yl)acetamido]ceph - 3 - em - 4 - car-  
boxylic acid (*syn* isomer),  
(6R,7R) - 3 - acetoxymethyl - 7 - [2 - (1 -  
carboxycyclobut - 1 - yloxyimino) - 2 -  
35 (fur - 2 - yl)acetamido]ceph - 3 - em -  
4 - carboxylic acid (*syn* isomer),  
(6R,7R) - 7 - [2 - (1 - carboxycyclobut - 1 -  
yloxyimino) - 2 - (fur - 2 - yl)acetamido] -  
3 - pyridiniummethylceph - 3 - em - 4 -  
40 carboxylic acid (*syn* isomer),  
(6R,7R) - 7 - [2 - (1 - carboxycyclobut -  
1 - yloxyimino) - 2 - (fur - 2 - yl)acet-  
amido] - 3 - (1 - methyltetrazol - 5 -  
ylthiomethyl)ceph - 3 - em - 4 - carboxylic  
acid (*syn* isomer),  
45 (6R,7R) - 3 - acetoxymethyl - 7 - [2 - (1 -  
carboxypropoxyimino) - 2 - (fur - 2 - yl)-  
acetamido]ceph - 3 - em - 4 - carboxylic  
acid (*syn* isomer),  
50 (6R,7R) - 3 - acetoxymethyl - 7 - [2 -  
(3 - carboxypent - 3 - yloxyimino) - 2 -  
(fur - 2 - yl)acetamido]ceph - 3 - em -  
4 - carboxylic acid (*syn* isomer),  
55 (6R,7R) - 3 - acetoxymethyl - 7 - [2 - (2 -  
carboxyprop - 2 - yloxyimino) - 2 - (thien -  
2 - yl)acetamido]ceph - 3 - em - 4 - car-  
boxylic acid (*syn* isomer), and non-toxic  
derivatives thereof, e.g. alkali metal salts  
such as the sodium or potassium salts.  
60 A further interesting class of cephalosporin  
antibiotics in accordance with the invention  
comprises compounds of general formula



[wherein R and W are as hereinbefore defined and p is 1 or 2] and non-toxic derivatives thereof. 65

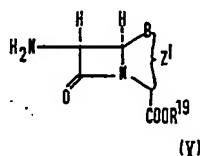
These compounds exhibit broad spectrum antibiotic activity coupled with high  $\beta$ -lactamase stability. A characteristic feature of the compounds is their high activity against strains of *Haemophilus influenzae* coupled with their particularly high activity against strains of *Escherichia coli* and *Proteus* organisms. 70

Especially preferred compounds of the above type, by virtue of their particularly high levels of activity against *Escherichia coli* and *Proteus* organisms, include the following:— 75

- (6R,7R) - 3 - acetoxymethyl - 7 - [2 - carboxymethoxyimino - 2 - (fur - 2 - yl)-acetamido]ceph - 3 - em - 4 - carboxylic acid (*syn* isomer), 80  
(6R,7R) - 3 - azidomethyl - 7 - [2 - carboxymethoxyimino - 2 - (fur - 2 - yl)-acetamido]ceph - 3 - em - 4 - carboxylic acid (*syn* isomer), 85  
(6R,7R) - 7 - [2 - carboxymethoxyimino - 2 - (fur - 2 - yl)acetamido] - 3 - (1 - methyltetrazol - 5 - ylthiomethyl)ceph - 3 - em - 4 - carboxylic acid (*syn* isomer), 90  
(6R,7R) - 7 - [2 - carboxymethoxyimino - 2 - (fur - 2 - yl)acetamido]ceph - 3 - em - 4 - carboxylic acid (*syn* isomer), and non-toxic derivatives thereof, e.g. alkali metal salts such as the sodium or potassium salts. 95

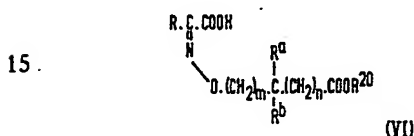
The compounds according to the invention may be prepared by any convenient method, for example by techniques analogous to those described in Belgian Patent No. 783449.

Thus according to one embodiment of the invention we provide a process for the preparation of an antibiotic compound of general formula I as hereinbefore defined or a non-toxic derivative thereof which comprises either (A) condensing a compound of the 100 formula 105



[wherein B is >S or >S→O ( $\alpha$ - or  $\beta$ -); R<sup>19</sup> represents hydrogen or a carboxyl blocking group, e.g. the residue of an ester-forming aliphatic or araliphatic alcohol or an ester- 110

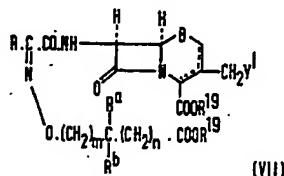
- forming phenol, silanol or stannanol (the said alcohol, phenol, silanol or stannanol preferably containing 1—20 carbon atoms) or a symmetrical or mixed anhydride group derived from an appropriate acid; and Z' is a group in which 2 carbon atoms link the nuclear sulphur atom and the 4-position carbon atom so that the compound possesses  $\Delta^2$  or  $\Delta^3$  unsaturation] or a salt, e.g. an acid addition salt such as a hydrochloride, hydrobromide, sulphatenitrate, phosphate, methane sulphonate or tosylate, or an N-silylated derivative thereof with an acylating agent corresponding to an acid of formula



- (wherein R, R<sup>a</sup>, R<sup>b</sup>, m and n are as hereinbefore defined and R<sup>20</sup> is a carboxyl blocking group, e.g. a group as hereinbefore defined in connection with R<sup>19</sup>); or (B), where Z in formula I is the group



(where Y is as hereinbefore defined) reacting a compound of the formula



- 25 (wherein B, R, R<sup>a</sup>, R<sup>b</sup>, m and n are as hereinbefore defined; each R<sup>19</sup> may independently represent hydrogen or a carboxyl blocking group; Y' is an atom or group which is replaceable by the residue of a nucleophile, e.g. an acetoxy or dichloroacetoxy group or a halogen atom such as chlorine, bromine or iodine; and the dotted line bridging the 2-, 3- and 4-positions indicates that the compound is a ceph - 2 - em or ceph - 3 - em compound) with a nucleophile; whereafter, if necessary and/or desired in each instance, any of the following reactions (C) in any appropriate sequence, are carried out:—
- 30 i) conversion of a  $\Delta^2$  isomer into the desired  $\Delta^3$  isomer,
- 40 ii) reduction of a compound wherein B is  $>S \rightarrow O$  to form a compound wherein B is  $>S$ ,
- iii) reduction of a 3-azidomethyl compound to form a 3-aminomethyl compound,
- 45 iv) acylation of a 3-aminomethyl compound to form a 3-acylaminomethyl compound,

- v) reaction of a 3-azidomethyl compound with a dipolarophile to form a compound having a polyazole ring linked to the 3-position carbon atom through a methylene group, 50
- vi) deacylation of a 3-acyloxymethyl compound to form a 3-hydroxymethyl compound, 55
- vii) acylation of a 3-hydroxymethyl compound to form a 3-acyloxymethyl compound,
- viii) carbamoylation of a 3-hydroxymethyl compound to form an unsubstituted or substituted 3-carbamoyloxymethyl compound, and 60
- ix) removal of carboxyl blocking groups; and finally (D) recovering the desired compound of formula I or a non-toxic derivative thereof, if necessary after separation of isomers. 65

Non-toxic derivatives of the compounds of formula I may be formed in any convenient way, for example according to methods well known in the art. Thus, for example, base salts may be formed by reaction of the cephalosporin acid with sodium 2-ethylhexanoate or potassium 2-ethylhexanoate. Biologically acceptable ester derivatives may be formed using conventional esterifying agents. 1-Oxides may be formed by treatment of the corresponding cephalosporin sulphide with an appropriate oxidising agent, for example with a peracid such as metaperiodic acid, peracetic acid, monoperphthalic acid or m-chloroperbenzoic acid, or with t-butyl hypochlorite, this last reagent conveniently being employed in the presence of a weak base such as pyridine. 70

75 Acylating agents which may be employed in the preparation of compounds of formula I include acid halides, particularly acid chlorides or bromides. Such acylating agents may be prepared by reacting an acid (VI) or a salt thereof with a halogenating agent e.g. phosphorus pentachloride, thionyl chloride or oxalyl chloride. Treatment of the sodium, potassium or triethylammonium salt of the acid (VI) with oxalyl chloride is advantageous in that under these conditions isomerisation is minimal. 80

85 Acylations employing acid halides may be effected in aqueous and non-aqueous reaction media, conveniently at temperatures of from  $-50$  to  $+50^\circ\text{C}$ , preferably  $-20$  to  $+30^\circ\text{C}$ , if desired in the presence of an acid binding agent. Suitable reaction media include aqueous ketones such as aqueous acetone, esters such as ethyl acetate, halogenated hydrocarbons such as methylene chloride, amides such as dimethylacetamide, nitriles such as acetonitrile, or mixtures of two or more such solvents. Suitable acid binding agents include tertiary amines (e.g. triethylamine or dimethylaniline), inorganic bases (e.g. calcium carbonate or sodium bicarbonate), and oxiranes such as lower 1,2-alkylene oxides (e.g. ethylene oxide 100 105 110



or propylene oxide) which bind hydrogen halide liberated in the acylation reaction.

Acids of formula VI may themselves be used as acylating agents in the preparation of compounds of formula I. Acylations employing acids (VI) are desirably conducted in the presence of a condensation agent, for example a carbodiimide such as N,N'-diethyl-, dipropyl- or diisopropylcarbodiimide, N,N'-dicyclohexylcarbodiimide or N-ethyl-N'-γ-dimethylaminopropylcarbodiimide; a carbonyl compound such as carbonyldiimidazole; or an isoxazolinium salt such as N-ethyl-5-phenylisoxazolinium perchlorate. Acylation reactions of this type are desirably effected in an anhydrous reaction medium, e.g. methylene chloride, dimethylformamide or acetonitrile.

Acylation may also be effected with other amide-forming derivatives of acids of formula VI such as, for example, a symmetrical anhydride or a mixed anhydride (e.g. with pivalic acid or formed with a haloformate such as a lower alkylhaloformate). The mixed or symmetrical anhydride may be generated *in situ*; thus, for example, a mixed anhydride may be generated using N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline. Mixed anhydrides may also be formed with phosphorus acids (for example phosphoric or phosphorous acids), sulphuric acid or aliphatic or aromatic sulphonic acids (for example *p*-toluene sulphonic acid).

It will be appreciated that in processes for the preparation of compounds of formula I wherein R<sup>a</sup> or R<sup>b</sup> represents carboxy it will in many instances be necessary to protect the carboxy group, for example by substitution with a carboxyl blocking group, e.g. a group as hereinbefore defined in connection with R<sup>19</sup>.

Any transformations of substituents at the 3-position which may be necessary in the preparation of particular compounds of formula I may, for example, be effected by methods described in the literature.

Thus, for example, compounds substituted at the 3-position by a group



wherein Y represents an ether or thioether group or a halogen atom may be prepared as described in British Patents Nos. 1,241,656; 1,241,657; 1,277,415 and 1,279,402. Compounds wherein Y is the residue of a nucleophile may also be prepared by the reaction of a 3-acetoxymethyl cephalosporin compound with a nucleophile, for example pyridine or other tertiary amine as described in British Patent No. 912,541; a sulphur-linking, nitrogen-linking or inorganic nucleophile as described in British Patent No. 1,012,943; a sulphur-linking nucleophile as described in

British Patents Nos. 1,059,562; 1,101,423 and 1,206,305; or a nitrogen-linking nucleophile as described in British Patents Nos. 1,030,630; 1,082,943 and 1,082,962. Compounds in which Y is a derivative of a residue of a nucleophile, e.g. where Y is an amino or acylamido group derived from an azido group may be prepared as described in British Patents Nos. 1,057,883 and 1,211,694, these patents further describing the reaction of compounds in which Y is azido with a dipolarophile. Compounds wherein Y is the residue of a nucleophile may also be prepared by the reaction of a 3-halomethylcephalosporin with any of the nucleophiles disclosed in the above references, such a process being described in British Patent No. 1,241,657, or by the reaction of a 3-halomethylcephalosporin sulphoxide with any of the nucleophiles disclosed in the above references, such a process being described in British Patent No. 1,326,531. The contents of the above mentioned British Patents are herein incorporated for reference purposes.

Where a 3-halomethylcephalosporin sulphide or sulphoxide ester is reacted with a tertiary nitrogen nucleophile such as pyridine in accordance with the process of British Patent No. 1,241,657 or 1,326,531, the reaction product will usually be obtained in the form of, for example, the corresponding 3-pyridiniummethyl halide. It has been observed that deesterification of compounds of this type by treatment with trifluoroacetic acid tends to promote isomerisation of the oxyimino moiety in the 7β-acylamido side chain; such isomerisation is clearly undesirable if a product containing at least 90% of the *syn* isomer is to be obtained without the need for a subsequent isomer separation stage.

It has also been observed, however, that the tendency to isomerisation may be substantially lessened if the 3-pyridiniummethyl halide is converted into the 3-pyridiniummethyl salt of a non-hydrohalic acid (e.g. trifluoroacetic, acetic, formic, sulphuric, nitric or phosphoric acid) prior to deesterification. Conversion of the halide salt into a non-hydrohalic acid salt is conveniently effected by means of anion exchange. This may be brought about by, for example, use of a suitable anion exchange resin, for example in the trifluoroacetate form. Where an anion exchange resin is employed, the 3-pyridiniummethyl halide may be run through a column of the resin prior to deesterification. It may be advantageous to employ an inert organic solvent system (i.e. one which does not have a harmful effect on the resin) to ensure adequate solubility for the cephalosporin compound; organic solvent systems which may be used include lower alkanols such as ethanol, ketones such as acetone, and nitriles such as acetonitrile.

Compounds possessing a 3-substituent.



wherein Y is a hydroxy group may be prepared by the methods described in British Patent No. 1,121,308 and Belgian Patent No. 841,937.

Where Y is a halogen (i.e. chlorine, bromine or iodine) atom, ceph - 3 - em starting compounds may be prepared by halogenation of a 7 $\beta$  - acylamido - 3 - methylceph - 3 - em - 4 - carboxylic acid ester 1 $\beta$ -oxide followed by reduction of the 1 $\beta$ -oxide group later in the sequence as described in British Patent No. 1,326,531. The corresponding ceph - 2 - em compounds may be prepared by the method of Dutch published Patent Application No. 6,902,013 by reaction of a 3 - methylceph - 2 - em compound with N-bromosuccinimide to yield the corresponding 3 - bromo - methylceph - 2 - em compound.

Carbamoylation of 3-hydroxymethyl compounds may be effected by conventional methods. Thus, for example, a 3-hydroxymethyl cephalosporin may be reacted with an isocyanate of formula R<sup>o</sup>.NCO (wherein R<sup>o</sup> represents a labile substituent group or an alkyl group) to give a compound containing a 3-position substituent having the formula  $-\text{CH}_2\text{O}.\text{CONHR}^o$  (wherein R<sup>o</sup> has the above defined meaning). Where R<sup>o</sup> is a labile substituent this substituent may if desired subsequently be cleaved, e.g. by hydrolysis, to form a 3-carbamoyloxymethyl group. Labile groups R<sup>o</sup> which are readily cleavable upon subsequent treatment include chlorosulphonyl and bromosulphonyl; halogenated lower alkanoyl groups such as dichloroacetyl and trichloroacetyl; and halogenated lower alkoxy carbonyl groups such as 2,2,2-trichloroethoxycarbonyl. These labile R<sup>o</sup> groups may generally be cleaved by acid or base catalysed hydrolysis (e.g. by base catalysed hydrolysis using sodium bicarbonate).

Another carbamoylating agent of use in the carbamoylation of 3-hydroxymethyl cephalosporins is cyanic acid, which is conveniently generated *in situ* from, for example, an alkali metal cyanate such as sodium cyanate, the reaction being facilitated by the presence of an acid, e.g. a strong organic acid such as trifluoroacetic acid. Cyanic acid effectively corresponds to a compound of formula R<sup>o</sup>.NCO wherein R<sup>o</sup> is hydrogen, and therefore converts 3-hydroxymethyl cephalosporin compounds directly to their 3-carbamoyloxymethyl analogues.

3-Hydroxymethyl cephalosporins for use in the above carbamoylation reactions may, for example, be prepared by the methods described in British Patent No. 1,121,308 and Belgian Patents Nos. 783,449 and 841,937.

Cephalosporin compounds possessing an acyloxymethyl group as 3-position substituent

may, for example, be prepared from a cephalosporin compound having a  $-\text{CH}_2\text{X}$  group (where X=OH or the residue of an acid HX which has a pKa of not more than 4.0, preferably not more than 3.5, as measured in water at 25°C) at the 3-position. X may thus, for example, represent chlorine, bromine, iodine, formyloxy, an acetoxy group having at least one electron-withdrawing substituent on the  $\alpha$ -carbon atom, or a nuclear substituted benzoyloxy group (the nuclear substituent being of the electron withdrawing type as described in British Patent No. 1,241,657), and the nucleophilic displacement reaction to form the desired 3-position acyloxymethyl may be carried out as described in our aforesaid British Patent No. 1,241,657. Alternatively, where X is hydroxy, a 3-acyloxymethyl cephalosporin may be obtained by acylation analogous with that described in British Patent No. 1,141,293, i.e. by aralkylating the 4-carboxy group, acylating the 3-hydroxymethyl group of the protected compound and subsequently removing the aralkyl group.

Compounds having a vinyl or substituted vinyl group at the 3-position may be obtained by the method described in Belgian Patent No. 761,897.

$\Delta^2$ -Cephalosporin ester derivatives obtained in accordance with the process of the invention may be converted into the corresponding  $\Delta^3$  derivative by, for example, treatment of the  $\Delta^2$  ester with a base.

Ceph - 2 - em reaction products may also be oxidised to yield the corresponding ceph - 3 - em 1-oxide, for example by reaction with a peracid as mentioned previously; the resulting sulphoxide may, if desired, subsequently be reduced as described hereinafter to yield the corresponding ceph - 3 - em sulphide.

Where a compound is obtained in which B is  $>\text{S}\rightarrow\text{O}$  this may be converted to the corresponding sulphide by, for example, reduction of the corresponding acyloxysulphonium or alkyloxysulphonium salt prepared *in situ* by reaction with e.g. acetyl chloride in the case of an acetoxysulphonium salt, reduction being effected by, for example, sodium dithionite or by iodide ion as in a solution of potassium iodide in a water miscible solvent e.g. acetic acid, tetrahydrofuran, dioxan, dimethylformamide or dimethylacetamide. The reaction may be effected at a temperature of  $-20^\circ$  to  $+50^\circ\text{C}$ .

Where a compound of formula I is obtained as a mixture of isomers, the *syn* isomer may be obtained by, for example, conventional methods such as crystallisation or chromatography. *Syn* and *anti* isomers may be distinguished by appropriate techniques, e.g. by their ultraviolet spectra, by thin layer or paper chromatography or by their proton magnetic resonance spectra. Thus, for example, the p.m.r. spectra of DMSO- $d_6$  solutions of *syn* compounds of Formula I exhibit the

doublet for the amide NH at a lower field than do similar solutions of the corresponding *anti*-isomers. These factors may be employed in monitoring reactions.

- 5 Starting materials of formula V wherein Z' is the group



- 10 may, for example, be prepared by the methods of Belgian Patent No. 774,480 and French Patent No. 2,165,834. Starting materials of formula V wherein Z' is a group of formula

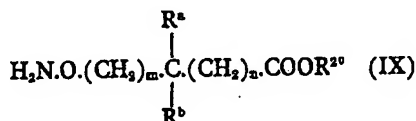


- 15 (where Hal represents a halogen atom such as fluorine, chlorine or bromine) may, for example, be prepared as described in German OLS No. 2,408,686.

Acids (VI) may be obtained by reacting a glyoxylic acid of formula

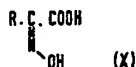


- 20 (where R has the above-defined meaning) or an ester thereof with a hydroxylamine derivative of formula

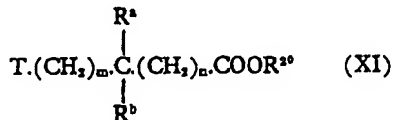


- 25 (where  $R^a$ ,  $R^b$ ,  $R^{20}$ ,  $m$  and  $n$  have the above-defined meanings). The resulting acid or ester may be separated into its *syn* and *anti* isomers by, for example, crystallisation, chromatography or distillation, whereafter ester derivatives may be hydrolysed to yield the corresponding acid.

- 30 Acids (VI) may also be prepared by etherification of an acid of formula



- 35 (where R has the above-defined meaning), e.g. by reaction with a compound of general formula

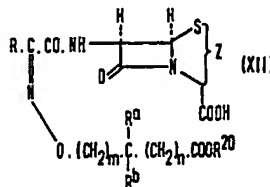


- 40 (wherein  $R^a$ ,  $R^b$ ,  $R^{20}$ ,  $m$  and  $n$  are as hereinbefore defined and T is halogen such as chloro, bromo or iodo; sulphate; or sulphonate such as tosylate). Separation of isomers

may be effected either before or after such etherification. The etherification reaction is desirably carried out in the presence of a base, e.g. potassium *t*-butoxide or sodium hydride, and is preferably conducted in an organic solvent, for example dimethylsulphoxide, a cyclic ether such as tetrahydrofuran or dioxan, or an N,N-disubstituted amide such as dimethylformamide. Under these conditions the configuration of the oximino group is substantially unchanged by the etherification reaction.

Acids of formula VI and acylating agents derived therefrom (e.g. acyl halides such as the chloride) are novel and comprise a feature of the present invention.

Derivatives of the compounds of the invention in which the carboxy substituent of the 7 $\beta$ -acylamido side chain is substituted by a carboxyl blocking group are also new and comprise a feature of the invention. These monoester derivatives, which may be represented by the general formula



(wherein R,  $R^a$ ,  $R^b$ , Z,  $m$  and  $n$  are as hereinbefore defined and  $R^{20}$  is a carboxyl blocking group such as *t*-butyl or diphenylmethyl), are of value as intermediates in the preparation of antibiotic compounds of general formula I. The compounds (XII) may themselves exhibit antibiotic activity, although generally at a very low level when compared to corresponding compounds (I).

Carboxyl blocking groups  $R^{20}$  and, where appropriate,  $R^{19}$  used in the preparation of compounds of formula I or in the preparation of necessary starting materials are desirably groups which may readily be split off at a suitable stage in the reaction sequence, conveniently as the last stage. It may, however, be convenient in some instances to employ biologically acceptable, metabolically labile carboxyl blocking groups such as acyloxymethyl groups (e.g. pivaloyloxymethyl) and retain these in the final product to give a biologically acceptable ester derivative of a compound of formula I.

Suitable carboxyl blocking groups are well known in the art, a list of representative blocked carboxyl groups being included in Belgian Patent No. 783,449. Preferred blocked carboxyl groups include aryl lower alkoxy-carbonyl groups such as *p*-methoxybenzyloxycarbonyl, *p*-nitrobenzyloxycarbonyl and diphenylmethoxycarbonyl; lower alkoxy-carbonyl groups such as *t*-butoxycarbonyl; and lower haloalkoxycarbonyl groups such as

2,2,2-trichloroethoxycarbonyl. The carboxyl blocking group may subsequently be removed by any of the appropriate methods disclosed in the literature; thus, for example, acid or base catalysed hydrolysis is applicable in many cases, as are enzymically-catalysed hydrolyses.

The antibiotic compounds of the invention, e.g. compounds of formula I and non-toxic derivatives thereof, may be formulated for administration in any convenient way, by analogy with other antibiotics and the invention therefore includes within its scope pharmaceutical compositions comprising an antibiotic compound in accordance with the invention adapted for use in human or veterinary medicine. Such compositions may be presented for use in conventional manner with the aid of any necessary pharmaceutical carriers or excipients.

The antibiotic compounds according to the invention may be formulated for injection and may be presented in unit dose form in ampoules, or in multi-dose containers with an added preservative. The compositions may take such forms as suspensions, solutions, or emulsion in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising and/or dispersing agents. Alternatively the active ingredient may be in powder form for reconstitution with a suitable vehicle, e.g. sterile, pyrogen-free water, before use.

The antibiotic compounds may also be presented in a form suitable for absorption by the gastro-intestinal tract. Tablets and capsules for oral administration may be in unit dose presentation form, and may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth or polyvinylpyrrolidone; fillers, for example lactose, sugar, maize-starch, calcium phosphate, sorbitol or glycine; lubricants, for example magnesium stearate, talc, polyethylene glycol or silica; disintegrants, for example potato starch; or acceptable wetting agents such as sodium lauryl sulphate. The tablets may be coated according to methods well known in the art. Oral liquid preparation may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparation may contain conventional additives such as suspending agents, for example sorbitol syrup, methyl cellulose, glucose/sugar syrup, gelatin, hydroxyethylcellulose, carboxymethyl cellulose, aluminium stearate gel or hydrogenated edible fats; emulsifying agents, for example lecithin, sorbitan mono-oleate or acacia; non-aqueous vehicles (which may include edible oils), for example almond oil, fractionated coconut oil, oily esters, propylene glycol

or ethyl alcohol; and preservatives, for example methyl or propyl p-hydroxybenzoates or sorbic acid. The antibiotic compounds may also be formulated as suppositories, e.g. containing conventional suppository bases such as cocoa butter or other glyceride.

Compositions for veterinary medicine may, for example, be formulated as intramammary preparations in either long acting or quick-release bases.

The compositions may contain from 0.1% upwards, e.g. 0.1—99%, preferably from 10—60% of the active material, depending on the method of administration. When the compositions comprise dosage units, each unit will preferably contain 50—1500 mg of the active ingredient. The dosage as employed for adult human treatment will preferably range from 500 to 5000 mg per day, depending on the route and frequency of administration, although in treating *Pseudomonas* infections higher daily doses may be required.

The antibiotic compounds according to the invention may be administered in combination with other therapeutic agents such as antibiotics, for example penicillins, tetracyclines or other cephalosporins.

The following examples illustrate the invention. All temperatures are in °C. The structure of the products were verified by p.m.r. spectroscopy (Preparations and Examples) and i.r. spectroscopy (Examples only).

#### Preparation 1.

2 - *t* - Butoxycarbonylmethoxyimino - 2 - (fur - 2 - yl)acetic acid (*syn isomer*)

The pH of a mixture of fur - 2 - yl glyoxylic acid (4.2 g), *t*-butoxycarbonylmethoxyamine (4.5 g) and water (50 ml) was adjusted to 5.0 with 2N sodium hydroxide solution. The resulting solution was stirred for 16 hours. The pH of the solution was increased to 7.0, and the solution was washed twice with ether. The aqueous solution was acidified to pH 1.8 under ether, and further extracted with ether. The combined ether extracts were washed (water, saturated brine), dried, and concentrated to give a solid (7.62 g), which was crystallised from carbon tetrachloride to give the *title compound* (3.67 g, 46%) m.p. 105.1—106.2°;  $\lambda_{\max}$  (pH6 phosphate buffer) 277.5 nm ( $\epsilon$  16,300).

#### Preparation 2.

2 - *t* - Butoxycarbonylmethoxyimino - 2 - (thien - 3 - yl)acetic acid (*syn isomer*)

Thien - 3 - yl glyoxylic acid and *t*-butoxycarbonylmethoxyamine were reacted as described in Preparation 1 to give the *title compound*, m.p. 102.6—104.4° (from carbon tetrachloride);  $\lambda_{\max}$  (pH6 phosphate buffer) 258 nm ( $\epsilon$  13,700).

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## Preparation 3.

- 2 - *RS* -  $\alpha$  - *t* - Butoxycarbonylbenzoyloxyimino - 2 - (fur - 2 - yl) acetic acid (*syn isomer*)
- 5 a)(i) A mixture of *N*-hydroxyphthalimide (24.5 g), anhydrous potassium carbonate (16.5 g), *t*-butyl  $\alpha$ -bromophenylacetate (41 g) and dimethylsulphoxide (225 ml) was stirred for 18 hours and was then poured into water (1.2 litres). The precipitated solid was filtered off, washed well with water, dried, and crystallised from industrial methylated spirits to give *N* - [ $\alpha$  - (*t* - butoxycarbonyl) benzoyloxy] phthalimide (41 g, 78%); m.p. 120.6—121.5°.
- 10 (ii) To a solution of the above oxyphthalimide (40 g) in dichloromethane (500 ml) was added 100% hydrazine hydrate (11.4 ml). A precipitate was formed immediately. The mixture was stirred for 1.5 hours, whereafter sufficient 5*N* ammonium hydroxide solution was added to dissolve the precipitate. The two layers were separated, and the aqueous layer was extracted once with methylene chloride. The combined organic extracts were washed (water, saturated brine), dried, and concentrated to give *t* - butyl  $\alpha$  - (aminooxy) - phenylacetate (25.0 g, 98% as colourless crystals, m.p. 48.2—49.6°).
- 20 b) Fur - 2 - yl glyoxylic acid and *t*-butyl  $\alpha$ -(aminooxy) phenylacetate were reacted as described in Preparation 1 to yield the *title compound* in 42% yield, m.p. 97.9—98.9° (from carbon tetrachloride);  $\lambda_{\max}$  (pH 6 phosphate buffer) 278 nm ( $\epsilon$  18,400).
- 35

## Preparation 4.

- 2 - *t* - Butoxycarbonylmethoxyimino - 2 - (thien - 2 - yl) acetic acid (*syn isomer*)
- 40 To a stirred suspension of sodium hydride (60% dispersion in oil, 0.96 g) in tetrahydrofuran (40 ml) was added 2 - hydroxyimino - 2 - (thien - 2 - yl) acetic acid (*syn isomer*) (1.71 g). The mixture was stirred for 30 minutes, after which time dimethylsulphoxide (25 ml) was added and stirring was continued for a further hour. *t*-Butyl chloroacetate (1.78 g) was added to the mixture, which was stirred for 16 hours and was then poured into water (300 ml). After being washed twice with ether, the aqueous phase was acidified to pH 1.7. Extraction with ether and concentration of the washed (water, saturated brine) and dried extracts gave a solid (2.71 g) which was crystallised from carbon tetrachloride to give the *title compound* (0.952 g, 33%), m.p. 88.3—91.3°;  $\lambda_{\max}$  (pH 6 phosphate buffer) 270.5 and 288.5 nm ( $\epsilon$  9,200 and 10,800).
- 55

## Preparation 5.

- 2 - (2 - *t* - Butoxycarbonylprop - 2 - yloxyimino) - 2 - (fur - 2 - yl) acetic acid (*syn isomer*)
- 60 A solution of 2 - (fur - 2 - yl) - 2 - hydroxyiminoacetic acid (*syn isomer*) (14.1 g) in dimethyl sulphoxide (100 ml) was added all at once to a magnetically stirred solution of potassium *t*-butoxide (22.4 g) in dimethyl sulphoxide (400 ml), the reaction mixture being maintained under an atmosphere of dry nitrogen. A gel was formed which, on stirring, became a finely divided, yellow solid. Stirring was continued for one hour, and then a solution of *t* - butyl 2 - bromo - 2 - methylpropionate (24.0 g) in dimethyl sulphoxide (50 ml) was added over one hour to the reaction mixture at room temperature. After addition was complete, the resulting solution was stirred for a further hour. The reaction was poured into ice-water (1.5 litres) and acidified under ether (500 ml) to pH 1.8 with concentrated hydrochloric acid. The two layers were separated, and the aqueous layer was extracted with more ether. The combined ether extracts were washed once with water, then extracted with aqueous sodium bicarbonate solution. The combined alkaline extracts were acidified under ether to pH 1.8 with concentrated hydrochloric acid, and the acid solution was extracted further with ether. The combined ether extracts were washed (water, saturated brine), dried, and concentrated to a yellow oil, which crystallised under high vacuum (22.41 g, 83%),  $\lambda_{\max}$  (EtOH) 272.5 nm ( $\epsilon$  15,400).
- 65 70 75 80 85 90 95
- The above solid (22.4 g) was crystallised from carbon tetrachloride (25 ml) to give the *title compound* (16.42 g, 61%), m.p. 72.5—74.2° (73.0°).

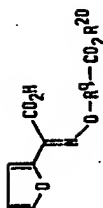
## Preparations 6—20.

- Method A
- 100 The dipotassium salt of 2 - (fur - 2 - yl) - 2 - hydroxyiminoacetic acid (*syn isomer*) was generated under an atmosphere of dry nitrogen and alkylated with the appropriate halo - *t* - butyl ester as described in Preparation 5. The products were isolated by pouring into water, acidifying, and extracting in the conventional manner.
- 105

## Method B

- 110 As method A but using a halo-diphenylmethyl ester.
- The half esters prepared by these methods are listed in Table 1.

TABLE 1



Preparation No.	R <sup>q</sup>	R <sup>20</sup>	Method	m.p. °C.	$\lambda_{\max}$ , nm (solvent)	$\epsilon$	$\tau$ values for d <sub>6</sub> -DMSO	
							R <sup>q</sup>	R <sup>20</sup>
6		-C(CH <sub>3</sub> ) <sub>3</sub>	A	69.8-73.4°	277 (pH6 buffer)	15,500	5.31; 8.56	8.58
7	-CH <sub>3</sub> - 	"	A	107°	271 (EtOH)	13,700	5.32	8.56
8		"	A	106.8-107.3°	277.5 (pH6 buffer)	15,100	8.03; 8.30	8.63
9		-CHPh <sub>2</sub>	B	102-104°	275 (EtOH)	12,700	5.1; 8.16; 8.7; 9.18	3.07 (CH)
10		"	B	—	271.5 (EtOH)	14,100	5.13; 8.11 9.07	3.09 (CH)
11		"	B	—	269 (EtOH)	13,200	8.08; 9.22	3.10 (CH)

\*Denotes (RS)-isomers

TABLE 1 (Continued)









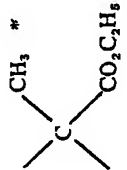
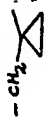
Preparation No.	R <sup>q</sup>	R <sup>∞</sup>	Method	m.p. °C.	λ <sub>max</sub> , nm (Solvent)	ε	r values (solvent)	
							R <sup>q</sup>	R <sup>∞</sup>
12	 CH(CH <sub>2</sub> ) <sub>2</sub> CH <sub>3</sub> *	-CHPh <sub>2</sub>	B	116-117°	270 (EtOH)	14,750	5.10; 7.9-8.9; 9.1 (d <sub>6</sub> -DMSO)	3.08 (CH)
13	 CH-  *	-CHPh <sub>2</sub>	B	—	270 (EtOH)	13,400	5.32; 7.8-9.2 (d <sub>6</sub> -DMSO)	3.07 (CH)
14	 CH-CH(CH <sub>2</sub> ) <sub>2</sub> *	-CHPh <sub>2</sub>	B	—	270.5 266.5 (EtOH)	13,700 13,250	5.14; 7.68; 8.95 9.15 (CDCl <sub>3</sub> )	3.05 (CH)
15	 CH-CH <sub>2</sub> CH-CH <sub>2</sub> *	-C(CH <sub>3</sub> ) <sub>3</sub>	A	77.0-80.3°	276.5 (pH6 buffer)	17,500	4.26; 4.86; 4.91 5.38; 7.44 (d <sub>6</sub> -DMSO)	8.60
16		"	A	91.5°	276.5 (pH6 buffer)	16,700	8.12; 8.50 (d <sub>6</sub> -DMSO)	8.57
17	 C(CH <sub>3</sub> ) <sub>2</sub> -C(CH <sub>3</sub> ) <sub>2</sub> -C(CH <sub>3</sub> ) <sub>2</sub>	"	A	91.5-93.8°	276 (pH6 buffer)	15,800	8.39; 8.56 (d <sub>6</sub> -DMSO)	8.56

TABLE 1 (Continued)

Preparation No.	R <sup>q</sup>	R <sup>20</sup>	Method	m.p. °C.	$\lambda_{\text{max}}$ , nm (solvent)	$\epsilon$	$\tau$ values d <sub>o</sub> -DMSO	
							R <sup>q</sup>	R <sup>20</sup>
18		-C(CH <sub>3</sub> ) <sub>3</sub>	A	113-114°	278 (pH 6 buffer)	17,200	7.4-8.3	8.59
19		"	A	+	-	-	5.76; 8.74; 8.33 (CH <sub>3</sub> )	8.54
20		-CHPh <sub>2</sub>	B	-	-	-	5.49; 8.6-8.9	3.15 (CH)

\*Denotes (R,S)-isomers

+N-benzyl-2-Phenylethylammonium salt mp. 129°



## Preparation 21.

2 - (2 - *t* - Butoxycarbonylprop - 2 - yloxyimino) - 2 - (thien - 2 - yl) acetic acid (*syn isomer*)

- 5 The title compound was prepared from 2 - hydroxyimino - 2 - (thien - 2 - yl)acetic acid (*syn isomer*) and *t*-butyl 2 - bromo - 2 - methylpropionate, in a similar manner to that described for Preparation 5, in 78%  
10 yield as a colourless oil, and was characterised as the *N* - benzyl - 2 - phenylethylammonium salt, m.p. 201.3—201.9° (from ethanol).

## Preparation 22.

- 15 2 - (2 - *t* - Butoxycarbonylethoxyimino) - 2 - (fur - 2 - yl)acetic acid (*syn isomer*)

To a mixture of methyl acetohydroxamic acid [CH<sub>3</sub>C(:NOH).OCH<sub>3</sub>] (8.9 g) and *t*-butyl acrylate (12.8 g) was added a solution of potassium *t*-butoxide (0.1 g) in *t*-butanol (1 ml). The mixture was kept at 0° for 65  
20 hours, then washed with water, dried, and distilled, to give 2 - *t* - butoxycarbonylethyl methyl acetohydroximate (2.37 g, 11%), b.p. 85—87°/1.2 mm Hg.

- 25 To a solution of fur - 2 - ylglyoxylic acid (1.26 g) in water (50 ml) was added 2 - *t* - butoxycarbonylethyl methyl acetohydroximate (2.15 g) and sufficient methanol to give a homogenous mixture, which was stirred for 30 minutes at pH 1.5. The pH was adjusted to 4.5 with 2*N* sodium hydroxide solution, and the mixture was stirred for a further 16 hours, when reaction was almost complete.  
30 Methanol was removed under reduced pressure, the pH of the residue was raised to 7.0, and the aqueous mixture was washed twice with ether. The aqueous phase was acidified in the presence of dichloromethane to pH 1.7, and the phases were separated. The aqueous phase  
40 was extracted twice more with dichloromethane. The combined dichloromethane extracts were washed with water, dried, and concentrated to give a fawn solid (1.53 g) (mixture of *syn* and *anti* isomers, 85:15) which was crystallised from carbon tetrachloride to give the title compound (0.975 g, 34%), m.p. 74.7—77.2°; λ<sub>max</sub> (pH6 buffer) 277 nm (ε 16,500).

## Preparation 23.

- 50 *t* - Butyl 1 - Bromocyclopentanecarboxylate  
To a mixture of 1-bromocyclopentanecarboxylic acid (36.99 g) and anhydrous ether

(35 ml) in a 500 ml pressure bottle, containing a magnetic stirrer-bar, was added concentrated sulphuric acid (3.5 ml), followed by precondensed isobutene (150 ml). The bottle was sealed, and stirred at ambient temperature for 20 hours. The bottle was then opened, excess isobutene was evaporated, and the residue in ether was washed with aqueous sodium bicarbonate solution and water, dried, and concentrated. The residue was distilled under reduced pressure to give the title ester (b.p. 66—74°/0.5—2.0 mm) (33.6 g, 70%); ν<sub>max</sub> (CHBr<sub>3</sub>) 1702 cm<sup>-1</sup>; τ (CDCl<sub>3</sub>) 7.78, 8.20 (cyclopentane protons) and 8.54 (C(CH<sub>3</sub>)<sub>3</sub>).

## Preparation 24.

Diphenylmethyl α-bromohexanoate  
α-Bromohexanoic acid (1.95 g) in light petroleum spirit (25 ml, b.p. 40—60°) was treated with a stock solution of diphenyldiazomethane in petroleum spirit (b.p. 40—60°) (ca. 3.8 mmole/10 ml) dropwise with stirring until a faint violet colour persisted. The mixture was stirred for 2 hours at room temperature, whereupon the solvent was removed *in vacuo*. The resulting oil in ethyl acetate was washed with a saturated aqueous solution of sodium bicarbonate then with water and dried. Removal of the solvent gave the title ester (3.0 g, 90%), λ<sub>max</sub> (EtOH) 252, 258, 263.5, 267.5 and 276 nm (ε 1650, 1600, 1350, 1150 and 850).

## Preparations 25—34.



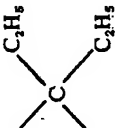



α-Halo Substituted Carboxylic Acid Esters  
Method A

The appropriate α-halo carboxylic acid was treated with isobutene and concentrated sulphuric acid in a pressure bottle at room temperature for 10—40 hours by the method described in Preparation 23 to give the *t*-butyl esters listed in Table 2.

## Method B




The appropriate α-halo carboxylic acid in a solvent (e.g. ether, petroleum, ethyl acetate) was treated with a solution of diphenyldiazomethane until a faint permanent colour was obtained. The ester was washed with alkali in the manner described in Preparation 24 to give the diphenylmethyl esters listed in Table 2.

TABLE 2  
X-R<sup>q</sup>-CO<sub>2</sub>R<sup>20</sup>

Preparation No.	X	R <sup>q</sup>	R <sup>20</sup>	Method	Ester $\nu_{\max}$ cm <sup>-1</sup> (CHBr <sub>3</sub> )	r values (solvent)	
						R <sup>q</sup>	R <sup>20</sup>
25	Cl	-CH <sub>2</sub> -	-C(CH <sub>3</sub> ) <sub>3</sub>	A	1735	4.06(CDCl <sub>3</sub> )	8.53
26	Br		"	A	1716	5.74; 8.22 (CDCl <sub>3</sub> )	8.51
27	Br	 *	-CHPh <sub>2</sub>	B	1737	5.29; 7.97; 9.07 (d <sub>6</sub> -DMSO)	3.10 (CH)
28	Br		"	B	1729	7.81; 9.10 (d <sub>6</sub> -DMSO)	3.06 (CH)
29	Br	 *	"	B	1730	5.24; 7.7-8.9; 9.12 (d <sub>6</sub> -DMSO)	3.09 (CH)
30	Br		"	B	1725, 1245	5.45, 7.8-9.3 (d <sub>6</sub> -DMSO)	3.04 (CH)
31	Br	 *	"	B	1738	5.40; 7.79; 9.0; 9.08 (d <sub>6</sub> -DMSO)	3.10 (CH)

\*Denotes (R,S)-isomers

TABLE 2 (Continued)

Preparation No.	X	R <sup>q</sup>	R <sup>20</sup>	Method	Ester $\nu_{\max} \text{ cm}^{-1}$ (CHBr <sub>3</sub> )	$\tau$ values (CHCl <sub>3</sub> )	
						R <sup>q</sup>	R <sup>20</sup>
32	Br		-C(CH <sub>3</sub> ) <sub>3</sub>	A	1710	7.9; 8.0-8.9	8.51
33	Br		"	A	1714	6.9-7.6; 7.7-8.3	8.52
34	Br		-CHPh <sub>2</sub>	B	—	6.29; 8.2-9.1	3.08 (CH)

## Preparation 35.

*Di-t-t-butyl 2-Bromo-2-methylmalonate*

- 5 To a stirred suspension of sodium hydride (1.7 g, 80% dispersion in oil) in tetrahydrofuran (60 ml) under an atmosphere of nitrogen was added di-t-t-butyl methylmalonate (11.52 g). The mixture was stirred at 60-70° for 1.5 hours to give a clear solution.
- 10 This solution was cooled to -25°, and to it was rapidly added a solution of bromine (2.6 ml) in dichloromethane (30 ml). The solution was allowed to warm to ambient temperature, then concentrated. The residue in ether was washed with water, dried, and fractionally distilled under reduced pressure to give the *title compound* b.p. 78-86°/1.0 mm Hg, (7.56 g, 49%);  $\nu_{\max}$  (CHBr<sub>3</sub>) 1730 cm<sup>-1</sup> (CO<sub>2</sub>Bu<sup>+</sup>);  $\tau$  (CDCl<sub>3</sub>) values include 8.05
- 15
- 20

(s, C(CH<sub>3</sub>)<sub>3</sub>) and 8.53 (2s, CH<sub>3</sub>, and C(CH<sub>3</sub>)<sub>3</sub>).

## Preparation 36.

- t-Butyl Ethyl 2-Bromo-2-methylmalonate*
- 25 The *title compound* was prepared in a similar manner to that used for the dibutyl ester in Preparation 35, in 83% yield, b.p. 64-68°/0.03 mm Hg.

## Preparation 37.

- 1-Bromomethylcyclopropane-1-carboxylic Acid*
- 30 The bromination of cyclobutane carboxylic acid led to the corresponding bromoacid together with the *title acid* (ca. 15% yield), m.p. 83-84° (petroleum spirit b.p. 60-80°);  $\tau$  (d<sub>6</sub>-DMSO) values 6.25, 8.65 and 8.90.
- 35

## Example 1.

- a) (6R,7R) - 3 - Acetoxymethyl - 7 - [2 - *t* - butoxycarbonylmethoxyimino - 2 - (fur - 2 - yl)acetamido]ceph - 3 - em - 4 - carboxylic acid (*syn isomer*)

Oxalyl chloride (0.45 ml) was added at 5° to a stirred solution of 2 - *t* - butoxycarbonylmethoxyimino - 2 - (fur - 2 - yl)acetic acid (*syn isomer*) (135 g) in dry dichloromethane (50 ml) containing triethylamine (0.7 ml) and dimethylformamide (1 drop). The solution was stirred at 5° for one hour and was then evaporated to dryness at 5°. The residue was suspended in acetone (50 ml) and was added over 30 minutes to a stirred, ice-cooled solution of (6R,7R) - 3 - acetoxymethyl - 7 - aminoceph - 3 - em - 4 - carboxylic acid (1.36 g) in water (100 ml) and acetone (50 ml) containing sodium bicarbonate (1.0 g). The reaction mixture was stirred for one hour, whereafter the acetone was evaporated under reduced pressure. The residue was acidified to pH 1.8, and this mixture was extracted with ether. The combined extracts were washed (water, saturated brine), dried, and evaporated to give the *title compound* (2.52 g, 96%) as a pale yellow foam,  $[\alpha]_D^{+28.5}$  (c 0.96, DMSO);  $\lambda_{max}$  (pH6 phosphate buffer) 276.5 nm (e 17,900).

- b) (6R,7R) - 3 - Acetoxymethyl - 7 - [2 - carboxymethoxyimino - 2 - (fur - 2 - yl) - acetamido]ceph - 3 - em - 4 - carboxylic acid, disodium salt (*syn isomer*)

A solution of (6R,7R) - 3 - acetoxymethyl - 7 - [2 - *t* - butoxycarbonylmethoxyimino - 2 - (fur - 2 - yl)acetamido]ceph - 3 - em - 4 - carboxylic acid (*syn isomer*) (1.422 g) and anisole (0.25 ml) in trifluoroacetic acid (5 ml) was kept at ambient temperature for 5 minutes. The mixture was concentrated at reduced pressure, ethyl acetate (10 ml) was added, and the mixture was re-evaporated. The residue was distributed between ether and sodium bicarbonate solution. The ether layer was extracted further with sodium bicarbonate solution and the combined alkaline extracts were acidified to pH 1.8 under ether. The acid mixture was extracted with ether, and the combined ether extracts were washed (water, saturated brine), dried, and evaporated to give the dicarboxylic acid corresponding to the *title compound* (942 mg, 74%),  $\tau$  (d<sub>6</sub>-DMSO) values include 0.24 (d, J 8Hz, NH), 4.13 (dd, 7-H), and 5.31 (s, CH<sub>2</sub>CO<sub>2</sub>H).

This di-acid (900 mg) in acetone (9 ml) was neutralised with a solution of sodium 2-ethylhexanoate (700 mg) in acetone (5 ml). The mixture was stirred for 10 minutes, then the precipitated solid was filtered off, washed with a little acetone, and dried to give the *title compound* (807 mg, 60%),  $[\alpha]_D^{+15}$

(c 1.08, DMSO);  $\nu_{max}$  (Nujol — registered Trade Mark) 1766 cm<sup>-1</sup> ( $\beta$ -lactam). 65

## Examples 2—23.

General Procedure for the Preparation of (6R,7R) - 7 - (2 - Aryl - 2 - carboxy - R<sup>a</sup> - oxyiminoacetamido) - 3 - (substituted) cephalosporin - 3 - em - 4 - carboxylic Acids (*syn isomers*) and/or their Salts 70

## Method A

Following the procedure described in Example 1, a solution of the appropriate 2 - aryl - 2 - *t* - butoxycarbonyl - R<sup>a</sup> - oxyiminoacetic acid (*syn-isomer*) (1 equiv) in methylene chloride optionally containing a few drops of N,N - dimethylformamide and triethylamine (1 equiv) was treated with oxalyl chloride (1 equiv) at 0—5° for ca. 1 hour. The mixture was then evaporated to dryness. The residue was suspended or dissolved in acetone and added to a stirred, ice-cold solution of (6R,7R) - 3 - acetoxymethyl - 7 - aminoceph - 3 - em - 4 - carboxylic acid (1—1.2 equiv) in water or a mixture of acetone and water containing sodium hydrogen carbonate (2—2.5 equiv). The reaction mixture was stirred for 0.5—2.5 hours, allowing the temperature to rise to room temperature, whereafter the acetone was removed under reduced pressure. The pH was adjusted to 1.5—2.0 and the product extracted into ethyl acetate (alternatively ether or methylene chloride may be used). The organic layer was washed with water and/or saturated brine, dried and evaporated to give the corresponding (6R,7R) - 3 - acetoxymethyl - 7 - (2 - aryl - 2 - *t* - butoxycarbonyl - R<sup>a</sup> - oxyiminoacetamide) - cephalosporin - 3 - em - 4 - carboxylic acid (*syn isomer*) which was characterised by optical rotation and/or by spectroscopy. 75 80 85 90 95 100

The *t*-butyl esters were deprotected by treating with trifluoroacetic acid containing anisole at room temperature for at least 5 minutes. The reaction mixture was evaporated *in vacuo* and the product isolated by trituration or by distributing between ethyl acetate (or ether) and an aqueous solution of sodium hydrogen carbonate, separating the aqueous extracts, acidifying these extracts under ethyl acetate and isolating the *title dicarboxylic acid* in the usual way. The products are listed in Table 3. 105 110 115

## Method B

As Method A except that the appropriate 2 - aryl - 2 - diphenylmethoxycarbonyl - R<sup>a</sup> - oxyiminoacetic acid (*syn-isomer*) was used in place of the *t*-butyl ester. The products are listed in Table 3. 120

## Method C

As Method A or B except that the dicarboxylic acid was converted into its disodium salt by treating a solution of the acid in 125

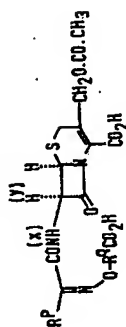
acetone with the solution of sodium 2-ethyl-7-aminocyclopent-2-en-1-carboxylate in acetone. The precipitated disodium salt was washed and dried. The products are listed in Table 3.

5 Method D

As Method A except that a (6R,7R) - 3 - (substituted methyl) - 7 - aminoceph - 3 - em - 4 - carboxylic acid or salt thereof was used in place of (6R,7R) - 3 - acetoxyethyl - 7 - aminoceph - 3 - em - 4 - carboxylic acid. 10

The products are listed in Table 4.

TABLE 3















Ex. No.	R <sup>P</sup>	R <sup>q</sup>	Salt	Method	[α] <sub>D</sub> (DMSO)	λ <sub>max</sub> , nm (pH 6 buffer)	ε	β-lactam ν <sub>max</sub> , cm <sup>-1</sup> (Nujol)	r values* for d <sub>6</sub> -DMSO at 100 MHz		
									x	y	R <sup>q</sup>
2		-CH <sub>2</sub> -	disodium	A, C	+26.5°	263	14,900	1762	0.15	4.10	5.32
3		-CH <sub>2</sub> -	-	A	+35°	292	10,200	1798	0.26	4.05	5.27
4			-	A	+48°	262	19,700	1778	0.13; 0.20	4.08; 4.16	4.28; 4.32 (CH) 2.3 - 2.6 (Ph)
5			disodium	A, C	+63°	275	16,800	1764	0.29	4.10	5.27 (CH) 8.54 (CH <sub>3</sub> )
6			disodium	A, C	+95°	274	16,800	1768	0.32	4.05	8.47

\*\*Denotes (RS)-isomers

\*Values for free acids









TABLE 3 (Continued)

Ex. No.	R <sup>p</sup>	R <sup>q</sup>	Salt	Method	[α] <sub>D</sub> (DMSO)	λ <sub>max</sub> , mμ (pH 6 buffer)	ε	β-lactam ν <sub>max</sub> , cm <sup>-1</sup> (Nujol)	τ values* for d <sub>6</sub> -DMSO at 100 MHz		
									x	y	R <sup>q</sup>
7			disodium	A, C	+62°	276	16,800	1756	0.38	4.10	7.90 and 8.28
8			disodium	A, C	+40°	276	15,400	1760	0.29	~4.15	4.1, ~4.8, 5.34, 7.38
9			disodium	A, C	+76.5°	275	15,500	1756	0.38	4.13	8.20, 8.50
10			—	A	+43°	274.5	10,100	1760	0.37	4.16	8.36
11			—	A, B	+28°	274	14,600	1780	0.31	4.09	7.56, 8.08
12			—	A	+21°	275.5	17,200	1790	0.33	4.16	5.80, 8.33, 8.80

\*\*Denotes (R,S)-isomers

\*Values for free acids

TABLE 3 (Continued)

Ex. No.		$R^p$	$R^q$	Salt	Method	$[\alpha]_D$ (DMSO)	$\lambda_{max}$ , nm (EtOH)	$\epsilon$	$\beta$ -lactam $\nu_{max}$ , $cm^{-1}$ (Nujol)	$r$ values* for $d_6$ -DMSO at 100 MHz		
										x	y	$R^q$
13		$>CH(CH_2)_3CH_3^{**}$		—	B	+45°	274	19,150	1771	0.31	4.11	5.40; 8.2; 8.6; 9.1
14		$>CHCH_2CH_3^{**}$		—	B	+57°	274	18,000	1776	0.35	4.10 4.13	5.45; 5.50 8.12; 9.01
15		$>C(C_2H_5)_2$		—	B	+44°	272.5	17,000	1773	0.41	4.16	8.1; 9.2
16		$>CH(CH_2)_2CH_3^{**}$		—	B	+53°	273	16,900	1780	0.37	4.10 4.12	5.40; 5.42 8.2; 8.5; 9.1
17		$>CH-$  $^{**}$		—	B	+41°	273	18,250	1782	0.4	4.18	5.65; 8.0 — 9.2
18		$>CHCH(CH_3)_2^{**}$		—	B	+69°	273	18,100	1781	0.38	4.14	5.61; 5.69 7.85; 9.0

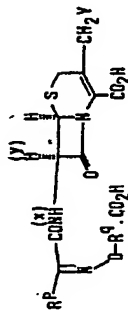
\*\*Denotes (RS)-isomers

\*Values for free acids

TABLE 3 (Continued)

No.	R <sup>p</sup>	R <sup>q</sup>	Salt	Method	[α] <sub>D</sub> (DMSO)	λ <sub>max</sub> , nm (pH 6 buffer)	ε	β-lactam ν <sub>max</sub> , cm <sup>-1</sup> (Nujol)	τ values* for d <sub>6</sub> -DMSO at 100 MHz		
									x	y	R <sup>q</sup>
19		$\text{C}(\text{CH}_3)_2$	—	A	+62.5°	262	13,900	1784	0.37	4.10	8.51
20		—CH <sub>2</sub> CH <sub>2</sub> —	—	A	+31°	276.5	15,800	1784	0.28	4.19	5.68; 7.34
21		—CH <sub>2</sub> —	—	B	+43°	276	17,250	1788	0.33	4.17	5.68; 8.7—9.0

TABLE 4



Ex. No.	R <sup>p</sup>	R <sup>q</sup>	Y	Salt	Method	[α] <sub>D</sub> (solvent)	λ <sub>max</sub> , nm (pH 6 buffer)	ε	β-lactam ν <sub>max</sub> , cm <sup>-1</sup> (Nujol)	τ* values for d <sub>6</sub> -DMSO at 100 MHz		
										x	y	R <sup>q</sup>
22		—CH <sub>2</sub> —	—N <sub>3</sub>	—	D	+35° (dioxan)	275	15,200	1770	0.14	4.10	5.31
23		—CH <sub>2</sub> —	—OCONH <sub>2</sub>	disodium	D	+47.5° (DMSO)	264	13,900	1770	0.25	4.13	5.33



## Example 24.

(6R,7R) - 7 - [2 - Carboxymethoxyimino - 2 - (fur - 2 - yl) - acetamido] - 3 - (1 - methyltetrazol - 5 - ylthiomethyl)ceph - 3 - em - 4 - carboxylic acid (*syn isomer*)

A solution of 2 - *t* - butoxycarbonylmethoxyimino - 2 - (fur - 2 - yl)acetic acid (*syn isomer*) (0.97 g) in methylene chloride (20 ml) was added dropwise at room temperature over 15 minutes to a stirred solution of diphenylmethyl (6R,7R) - 7 - amino - 3 - (1 - methyltetrazol - 5 - ylthiomethyl)ceph - 3 - em - 4 - carboxylate (1.484 g) and dicyclohexylcarbodiimide (0.743 g) in methylene chloride (45 ml). After stirring for a further 2 hours the solvent was removed by evaporation, and the residue was stirred for 5 minutes with ethyl acetate (50 ml) and filtered. The filtrate was washed with saturated sodium bicarbonate solution, diluted with an equal volume of water and then with brine (25 ml of each), dried and evaporated to a foam (2.5 g) which was dissolved in benzene and purified by chromatography on Kieselgel (70 g). Elution with benzene:ethyl acetate (10:1), combination of appropriate fractions and evaporation to dryness gave a foam (2.05 g) which was dissolved in ethyl acetate and run into light petroleum to give diphenylmethyl (6R,7R) - 7 - [2 - *t* - butoxycarbonylmethoxyimino - 2 - (fur - 2 - yl) - acetamido] - 3 - (1 - methyltetrazol - 5 - ylthiomethyl)ceph - 3 - em - 4 - carboxylate (*syn isomer*) (2.02 g, 90%) as a white amorphous solid,  $[\alpha]_D^{25} - 102^\circ$  (*c* 0.99, CHCl<sub>3</sub>);  $\lambda_{max}$  (EtOH) 278 nm ( $\epsilon$  19,800).

A solution of this diester (1.93 g) in a mixture of trifluoroacetic acid (7.7 ml) and anisole (1.9 ml) was kept at 0° for 10 minutes and then added to a mixture of saturated sodium bicarbonate and water (1:3, 850 ml). After stirring for 10 minutes the mixture was washed with ethyl acetate, covered with more ethyl acetate (200 ml) and acidified to pH 2 with concentrated hydrochloric acid. The organic phase was separated, washed with water and brine, dried and evaporated to a foam (1.54 g). Thin layer chromatography suggested that deprotection was incomplete and the product was retreated with trifluoroacetic acid (4.3 ml) and anisole (1.1 ml) at 20° for 15 minutes, whereafter the product was isolated as a foam (1.3 g) as described above. This foam in ethyl acetate was run into light petroleum to give the *title dicarboxylic acid* (0.8 g, 59%) as a white amorphous solid,  $[\alpha]_D^{25} - 99^\circ$  (*c* 1.05, acetone);  $\lambda_{max}$  (0.1M-pH 6 phosphate buffer) 277 nm ( $\epsilon$  21,900);  $\nu_{max}$  (Nujol) 1780 cm<sup>-1</sup>;  $\tau$  (d<sub>6</sub>-DMSO) values include 0.19 (d, NH), 4.14 (dd, 7-H), 5.30 (s, CH<sub>2</sub>CO<sub>2</sub>H).

## Examples 25—36.

General Procedure for the Preparation of (6R,7R) - 7 - [2 - carboxy - R<sup>a</sup> - oxyimino - 2 - (fur - 2 - yl)acetamido] - 3 - (substituted) - ceph - 3 - em - 4 - carboxylic acids (*syn isomers*) using Dicyclohexylcarbodiimide

(i) To a solution of a diphenylmethyl (6R,7R) - 7 - amino - 3 - (substituted)ceph - 3 - em - 4 - carboxylate (1 equiv) and dicyclohexylcarbodiimide (1—1.3 equiv) in dry methylene chloride was added at 0—25° a solution of the appropriate 2 - *t* - butoxycarbonyl - R<sup>a</sup> - oxyimino - 2 - (fur - 2 - yl)acetic acid (*syn isomer*) (1—1.15 equiv) in dry methylene chloride. After stirring for 0.5—5.0 hours the dicyclohexylurea was removed by filtration and the filtrate was evaporated. The residue in ethyl acetate or methylene chloride was washed successively with aqueous sodium bicarbonate, water and brine, dried and evaporated. The diester was purified by chromatography on silica or, after decolourisation with charcoal, by trituration or crystallisation. The product was characterised by its p.m.r. spectrum and by thin layer chromatography.

Where the 7-amino starting material was available as an acid addition salt the free base was liberated by shaking with a mixture of ethyl acetate (or methylene chloride) and an excess of an aqueous solution of sodium bicarbonate. After washing with water and brine the organic layer was evaporated to dryness and the free amine used as described above.

(ii) *Method A.* The intermediate diesters so derived were deprotected by dissolving in a mixture of trifluoroacetic acid (3—10 ml/1 g of diester) and anisole (0.8—12 ml/1 g of diester) and left at between 0° and room temperature for between 5 minutes and 2.5 hours. The mixture was concentrated under reduced pressure and added to a mixture of ethyl acetate or ether and excess aqueous sodium bicarbonate, and the aqueous layer was washed with ethyl acetate. The aqueous phase was covered with ethyl acetate and acidified to pH 1—2 with hydrochloric acid. The organic layer was washed, dried and evaporated to give the required dicarboxylic acid.

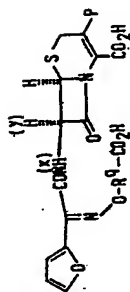
(ii) *Method B.*

In some cases where treatment with trifluoroacetic acid was insufficient to complete deprotection the intermediate monoester (usually the *t*-butoxycarbonyl group was cleaved more slowly than the diphenylmethoxycarbonyl group) was retreated with trifluoroacetic acid and anisole and the diacid isolated as described above.

## (iii) Method C.


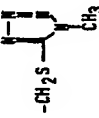



The 3-carboxyvinyl derivative described in Example 36 was prepared from a 7-amino derivative in which both carboxy groups were protected as the diphenylmethyl ester. The resulting triester was deprotected as in Method B to provide the required tricarboxylic acid. The properties of the reaction products are listed in Table 5.

TABLE 5



Ex. No.	R <sup>q</sup>	P	Method	[α] <sub>D</sub> (solvent)	λ <sub>max</sub> , nm (solvent)	ε	β-lactam ν <sub>max</sub> , cm <sup>-1</sup> (Nujol)	r values for d <sub>6</sub> -DMSO at 100 MHz		
								x	y	R <sup>q</sup>
25			B	-12° (H <sub>2</sub> O)	278 (pH 6 buffer)	20,050	1781	0.33	4.1	8.51
26	-CH <sub>3</sub> -	-CH=CHCO <sub>2</sub> CH <sub>3</sub> (trans)	B	-108° (aq. NaHCO <sub>3</sub> )	295 (pH 6 buffer)	26,200	1775	0.20	4.08	5.32
27			A	-48° (DMSO)	278 (pH 6 buffer)	21,800	1780	0.38	4.1	8.49; 8.57
28	C(CH <sub>3</sub> ) <sub>2</sub>	Cl	B	+92.5° (CHCl <sub>3</sub> )	272.5 (EtOH)	16,600	1780	0.34	4.11	8.51
29			A	-89° (DMSO)	221 283 (pH 6 buffer)	23,900 21,550	1772	0.42	4.10	7.9; 8.3

TABLE 5 (Continued)

Ex. No.	R <sup>q</sup>	P	Method	[α] <sub>D</sub> (solvent)	λ <sub>max</sub> , nm (solvent)	ε	β-lactam ν <sub>max</sub> , cm <sup>-1</sup> (Nujol)	r values for d <sub>6</sub> -DMSO at 100 MHz		
								x	y	R <sup>q</sup>
30		-CH-CHCO <sub>2</sub> C <sub>4</sub> H <sub>9</sub> (trans)	B	-8° (aq. NaHCO <sub>3</sub> )	295 (pH 6 buffer)	26,200	1780	0.38	4.09	7.9; 8.3
31	"	-CH-CHCO <sub>2</sub> H (trans)	C	-15° (aq. NaHCO <sub>3</sub> )	294.5 (pH 6 buffer)	31,200	1779	0.38	4.07	7.9; 8.3
32	"		A	-71° (CHCl <sub>3</sub> )	279 (pH 6 buffer)	22,000	1780	0.42	4.15	7.9; 8.28
33	"	-CH-CHCO <sub>2</sub> CH <sub>3</sub> (trans)	B	-85° (5% NaHCO <sub>3</sub> )	295 (pH 6 buffer)	26,800	1780	0.33	4.05	7.90; 8.25
34		-CH-CHCO <sub>2</sub> CH <sub>3</sub> (trans)	B	-104.4° (5% NaHCO <sub>3</sub> )	295 (pH 6 buffer)	27,200	1779	0.34	4.09	8.52; 8.60
35	-CH <sub>2</sub> - 	H	B	+84° (5% NaHCO <sub>3</sub> )	281.5 (pH 6 buffer)	15,100	1774	0.19	4.08	5.31
36		H	B	+162° (5% NaHCO <sub>3</sub> )	283 (pH 6 buffer)	13,800	1775	0.37	4.05	7.9; 8.25

## Example 37.

(6R,7R) - 7 - [2 - (1 - Carboxycyclopent - 1 - yloxyimino) - 2 - (fur - 2 - yl)acetamido]ceph - 3 - em - 4 - carboxylic acid (syn isomer)

5 a) A stirred solution of diphenylmethyl (6R,7R) - 7 - aminoceph - 3 - em - 4 - carboxylate (5.50 g) and propylene oxide (5.23 g) in dry methylene chloride (100 ml) at -5° was treated dropwise, over 20 minutes, with a solution of 2 - (1 - t - butoxycarbonylcyclopent - 1 - yloxyimino) - 2 - (fur - 2 - yl) - acetyl chloride (syn isomer) in methylene chloride (see below). The resulting solution was stirred at 0° for 40 minutes and allowed to warm to 22° while stirring for a further hour. Methanol (15 ml) was added and the stirring continued for 15 minutes. The solution was washed with 2N - hydrochloric acid, saturated aqueous sodium bicarbonate and saturated brine. After drying and clarification with charcoal evaporation afforded a foam, which was dissolved in ether and added dropwise to petroleum-ether to give 25 diphenylmethyl (6R,7R) - 7 - [2 - (1 - t - butoxycarbonylcyclopent - 1 - yloxyimino) - 2 - (fur - 2 - yl) - acetamido]ceph - 3 - em - 4 - carboxylate (syn isomer) as a colourless powder (8.3 g, 83%);  $[\alpha]_D^{+43}$  (c 0.1, CHCl<sub>3</sub>);  $\lambda_{max}$  (EtOH) 277 nm (ε 17,300).

30 (b) The diester prepared in (a) above (6 g) in anisole (30 ml) at 0° was treated with trifluoroacetic acid (24 ml) and the solution was stirred for 30 minutes. The reaction mixture was allowed to reach 22° while stirring for a further 2 hours, and was then concentrated in *vacuo* to ca 20 ml. The residual oil was partitioned between ethyl acetate and saturated aqueous sodium bicarbonate. The organic layer was extracted with bicarbonate solution and the combined alkaline layers were washed with ethyl acetate and ether. The aqueous layer was covered with ethyl acetate and adjusted to pH 1.5 with concentrated 45 hydrochloric acid. The resulting organic layer was washed with saturated brine, dried and evaporated to a foam which contained the title acid.

50 The foam was dissolved in a buffer containing 0.1 M sodium acetate, 0.1 M acetic acid and 0.2 M sodium chloride (75 ml) with the aid of sodium bicarbonate. The solution was treated with Amberlite (registered Trade Mark) XAD-8 (50 ml) and adjusted to pH 4.8 with 2N-hydrochloric acid. The resulting stirred suspension was treated with Woelm neutral alumina (20 g) while the pH was maintained at 4.8. The suspension was stirred for 20 minutes and was loaded on a column above Woelm neutral alumina (25 g). The title acid was eluted with the aforementioned buffer (300 ml) and with 2% aqueous sodium acetate (500 ml). The eluates were freeze-dried and redissolved in the minimum volume of water. After adjustment to pH 1.5 65

with concentrated hydrochloric acid, the acidic liquors were extracted with ethyl acetate and the combined extracts were dried and evaporated to give a foam. On trituration with ethyl acetate, petroleum and ether the title acid was obtained as a colourless solid (3.5 g, 88%);  $[\alpha]_D^{+162}$  (c 0.01, 5% aqueous NaHCO<sub>3</sub>);  $\lambda_{max}$  (pH 6 phosphate buffer) 282 nm (ε 14,000);  $\nu_{max}$  (Nujol) 1775 (β-lactam), 1710 (CO<sub>2</sub>H), and 1680 and 1528 cm<sup>-1</sup> (CONH);  $\tau$  (DMSO-d<sub>6</sub>) values include 0.37 (d, J 8Hz, CONH), 2.10, 3.24 and 3.31 (m, furyl protons), 4.05 (dd, J 5 and 8 Hz, 7-H), 4.80 (d, J 5 Hz, 6-H), and 7.90 and 8.25 (2 x broad m, cyclopentyl protons). The p.m.r. spectrum also showed the presence of  $\frac{1}{2}$  mol each of ethyl acetate and water.

The acylating agent used in step (a) above was made as follows:—

85 A stirred suspension of phosphorus pentachloride (3.75 g) in dry methylene chloride (120 ml) and dimethylacetamide (6.53 g) at -10° was treated with 2 - (1 - t - butoxycarbonylcyclopent - 1 - yloxyimino) - 2 - (fur - 2 - yl) acetic acid (syn isomer) (5.82 g) in small portions to maintain the temperature below -5°. After stirring for 15 minutes the solution was treated with ice (40 g) and stirred for 20 minutes to give 95 the corresponding acid chloride in the organic layer.

## Examples 38—42.

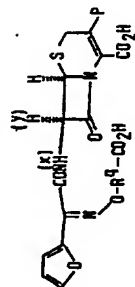
General Procedure for the Preparation of (6R,7R) - 3 - (Optionally substituted) - 7 - [2 - (carboxy - R<sup>a</sup> - oxyimino) - 2 - (fur - 2 - yl)acetamido] - ceph - 3 - em - 4 - carboxylic Acids (syn-isomers) by Treating an Ester of a (6R,7R) - 3 - (Optionally substituted) 7 - aminoceph - 3 - em - 4 - carboxylic Acid with an Acid Chloride (syn-isomer)

100 A 2 - (t - butoxycarbonyl - R<sup>a</sup> - oxyimino) - 2 - (fur - 2 - yl)acetic acid (syn-isomer) was converted into its acid chloride as described for Examples 2—23. A solution of the acid chloride (1—1.3 equiv) in methylene chloride was added dropwise at -5° to +5° over a period of 10—30 minutes to a solution of diphenylmethyl (6R,7R) - 3 - (optionally substituted) - 7 - aminoceph - 3 - em - 4 - carboxylate (1 equiv) in dry methylene chloride containing propylene oxide (5—20 equiv). The reaction mixture was stirred for ca 1—3 hours at 0° to room temperature and then washed successively with 2N-hydrochloric acid, aqueous sodium bicarbonate, water and/or brine. The dried organic layer was evaporated and the residue purified by trituration, precipitation, chromatography or crystallisation. 125

The resulting diphenylmethyl (6R,7R) - 3 - (optionally substituted) - 7 - [2 - (t -

butoxycarbonyl - R<sup>q</sup> - oxyimino) - 2 - (fur - 2 - yl)acetamido]ceph - 3 - em - 4 - carboxylate (*syn* isomer) was deprotected as described in Table 6.

TABLE 6



Ex. No.	R <sup>q</sup>	P	Method	[α] <sub>D</sub> (solvent)	λ <sub>max</sub> , nm (pH 6 buffer)	ε	β-lactam ν <sub>max</sub> , cm <sup>-1</sup> (Nujol)	r values for d <sub>6</sub> -DMSO at 100 MHz		
								x	y	R <sup>q</sup>
38	-CH <sub>2</sub> -	-CH-CHCO <sub>2</sub> Et (trans)	B	-	294.5	26,300	1780	0.12	4.04	5.30
39	-CH <sub>2</sub> -	-CH-CHCN	B	-	291.5	21,800	1785	0.08	4.01	5.29
40	-CH <sub>2</sub> -		A	-38° (DMSO)	277.5	23,600	1775	0.21	4.19	5.30
41		-H	B	+113° (aq. NaHCO <sub>3</sub> )	279.5	13,400	1777	0.41	4.09	8.5
42			A	-97.3° (CHCl <sub>3</sub> )	279	21,900	1782	0.32	4.11	7.6; 8.1

## Example 43.

(a) (6R,7R) - 3 - Benzoyloxymethyl - 7 - [2 - (2 - t - butoxycarbonylprop - 2 - yloxyimino) - 2 - (fur - 2 - yl)acetamido] - ceph - 3 - em - 4 - carboxylic acid (*syn isomer*)

A suspension of phosphorus pentachloride (313 mg) in dry dichloromethane (4 ml) at  $-10^{\circ}$  was treated with N,N-dimethylacetamide (0.7 ml) followed by 2 - (2 - t - butoxycarbonylprop - 2 - yloxyimino) - 2 - (fur - 2 - yl) acetic acid (*syn isomer*) (446 mg) portionwise. The resulting solution was stirred at  $-10^{\circ}$  for 30 minutes, treated with ice (ca 1 g) and stirred at below  $0^{\circ}$  for 15 minutes. The organic phase was added dropwise to a solution of (6R,7R - 7 - amino - 3 - benzoyloxymethylceph - 3 - em - 4 - carboxylic acid (502 mg) in N,N-dimethylacetamide (2 ml) and acetonitrile (2 ml) containing triethylamine (1.09 ml) at below  $0^{\circ}$ . The solution was stirred at  $0^{\circ}$  to  $5^{\circ}$  for 2 hours, methanol (0.3 ml) was added, and stirring was continued for 15 minutes. The solution was diluted with dichloromethane (20 ml) and washed successively with 2N-hydrochloric acid, water and brine, dried and evaporated to a gum (1.02 g). A solution of this gum in ethyl acetate (6 ml) was run dropwise into stirred petroleum ether (b.p.  $40-60^{\circ}$ , 200 ml) to give the *title acid* as a cream powder (769 mg, 83%);  $[\alpha]_D^{+26}$  (*c* 1.05, acetone);  $\lambda_{max}$  (pH 6 phosphate buffer) 233.5 nm ( $\epsilon$  19,200) and 274 nm ( $\epsilon$  18,600);  $\nu_{max}$  (Nujol)  $1790\text{ cm}^{-1}$  ( $\beta$ -lactam);  $\tau$  ( $d_6$ -DMSO) values include 0.29 (d, J 8 Hz, NH), 4.03 (dd, J 8 and J 5 Hz, 7-H), 8.50 (s, C(CH<sub>3</sub>)<sub>2</sub>) and 8.58 (s, C(CH<sub>3</sub>)<sub>2</sub>).

(b) (6R,7R) - 3 - Benzoyloxymethyl - 7 [2 - (2 - carboxyprop - 2 - yloxyimino) - 2 - (fur - 2 - yl)acetamido]ceph - 3 - em - 4 - carboxylic acid (*syn isomer*)

A solution of (6R,7R - 3 - benzoyloxymethyl - 7 - [2 - (2 - t - butoxycarbonylprop - 2 - yloxyimino) - 2 - (fur - 2 - yl)acetamido] - ceph - 3 - em - 4 - carboxylic acid (*syn isomer*) (620 mg) in anisole (0.6 ml) and trifluoroacetic acid (3 ml) was stirred at  $20^{\circ}$  for 25 minutes. The solution was partitioned between ethyl acetate and aqueous sodium bicarbonate solution and the pH adjusted to pH 8 by addition of solid sodium bicarbonate. The aqueous phase was separated, washed with ethyl acetate, covered with ethyl acetate, and the pH adjusted to pH 1.5 by addition of concentrated hydrochloric acid. The organic phase was separated, washed successively with water and brine, dried and evaporated to an oily foam (584 mg). A solution of this foam in ethyl acetate was run dropwise into stirred petroleum ether (b.p.  $40-60^{\circ}$ ) to give the *title dicarboxylic acid* as an off-white solid (384 mg, 67%);  $[\alpha]_D^{+}$

$30.4^{\circ}$  (*c* 1.0, acetone);  $\lambda_{max}$  (pH phosphate buffer) 234 nm ( $\epsilon$  19,700) and 273 nm ( $\epsilon$  18,450);  $\nu_{max}$  (Nujol)  $1784\text{ cm}^{-1}$  ( $\beta$ -lactam);  $\tau$  ( $d_6$ -DMSO) values include 0.30 (d, J 8 Hz, NH), 4.07 (dd, J 8 and J 5 Hz, 7-H), and 8.50 (s, C(CH<sub>3</sub>)<sub>2</sub>).

## Example 44.

Potassium (6R,7R) - 7 - [2 - carboxymethoxyimino - 2 - (fur - 2 - yl) acetamido] - 3 - pyridiniummethyl - ceph - 3 - em - 4 - carboxylate (*syn isomer*)

A mixture of (6R,7R) - 3 - acetoxymethyl - 7 - [2 - carboxymethoxyimino - 2 - (fur - 2 - yl)acetamido]ceph - 3 - em - 4 - carboxylate (*syn isomer*) (3.26 g), potassium thiocyanate (5.25 g), pyridine (0.72 ml) and water (2 ml) was stirred and heated for 40 minutes at  $80^{\circ}$ . The cooled reaction mixture was diluted with water (5 ml) and adsorbed on a column of XAD-2 resin (500 g). Components of the reaction mixture were eluted, first with water and then with aqueous ethanol (1:3) and collected using an automatic fraction collector. Those fractions having the characteristic ultraviolet absorption pattern of the required product were combined and evaporated to dryness *in vacuo* at  $<35^{\circ}$ . The crude material (600 mg) was crystallized from aqueous acetone (1:9) to give the *title compound* (295 mg);  $\lambda_{max}$  (pH 6 phosphate buffer) 261 nm ( $\epsilon$  19,000);  $\lambda_{min}$  275 nm ( $\epsilon$  18,400).

## Example 45.

Potassium (6R,7R) - 7 - [2 - carboxyprop - 2 - yloxyimino - 2 - (fur - 2 - yl) - acetamido] - 3 - pyridiniummethyl - ceph - 3 - em - 4 - carboxylate (*syn isomer*)

A mixture of (6R,7R) - 3 - acetoxymethyl - 7 - [2 - (carboxyprop - 2 - yloxyimino) - 2 - (fur - 2 - yl)acetamido]ceph - 3 - em - 4 - carboxylic acid (*syn isomer*) (4.0 g), pyridine (4 ml) and water (40 ml) was heated for 1 hour at  $80^{\circ}$ , whereafter the mixture was allowed to cool. The cooled mixture was diluted with water (50 ml) and extracted five times with methylene chloride (25 ml) and the combined organic extracts were washed with water. The combined aqueous phases were evaporated *in vacuo* at  $<35^{\circ}$  to ca 50 ml and acidified to pH 2 with 2N-hydrochloric acid. The precipitated solid was removed by filtration, the filtrate was adjusted to pH 6.5 with potassium bicarbonate and the solution was concentrated *in vacuo* at  $<35^{\circ}$  to ca. 40 ml. The product was purified on a column of XAD-2 resin (500 g), elution being effected with water and then aqueous ethanol (1:3). Fractions having the characteristic ultraviolet absorption of the product were combined and evaporated to dryness *in vacuo* at  $<35^{\circ}$  to give the *title compound* (880 mg);  $\lambda_{max}$  (H<sub>2</sub>O) 261 and 277 nm ( $\epsilon$  17,000 and 16,950).

## Example 46.

Sodium (6R,7R) - 7 - [2 - (carboxyprop - 2 - yloxyimino) - 2 - (fur - 2 - yl) - acetamido] - 3 - pyridiniummethylceph - 3 - em - 4 - carboxylate (*syn* isomer)

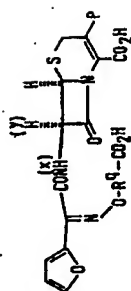
A mixture of sodium iodide (50.0 g), water (15.5 ml) and pyridine (14 ml) was heated to 80° and stirred vigorously during the addition over a period of *ca* 10 minutes of (6R,7R) - 3 - acetoxymethyl - 7 - [2 - carboxyprop - 2 - yloxyimino) - 2 - (fur - 2 - yl)acetamido]ceph - 3 - em - 4 - carboxylate (*syn* isomer) (14.4 g). The mixture was stirred at 80° for a total of 55 minutes and was then cooled and diluted to *ca* 400 ml with water. 0.1 N-Sodium hydroxide was added to adjust the pH to *ca* 6.5 and the solution was concentrated under reduced pressure at <40° to a volume of *ca* 100 ml. The resulting solution was diluted to *ca* 400 ml with water, methyl isobutyl ketone (0.3 ml) was added and the stirred solution was acidified with 2N-hydrochloric acid (15 ml) to achieve a pH of 1—2. The solid was collected, washed with water and discarded. The filtrate and washings were treated with more 2N-hydrochloric acid (*ca* 10 ml) and extracted with ethyl acetate, the organic layer being re-extracted with a small volume of water. The aqueous phase was adjusted to pH 6 with 1N-sodium hydroxide (*ca* 43 ml) and evaporated under reduced pressure at <40° to a volume of *ca* 175 ml. This solution was

applied to a column of XAD-2 resin (700 g, 42 cm × 5.5 cm) that had previously been washed with water (2 litres). The column was eluted with water, the fractions being collected automatically and monitored by U.V. spectroscopy. When the inorganic salts and some impurities had been removed the eluant was changed to a mixture of ethanol and water (1:4). The fractions having the characteristic U.V. absorption of the product were combined, concentrated under reduced pressure at <40° then freeze-dried. The product was dried over phosphorus pentoxide *in vacuo* giving the *title salt* (4.10 g);  $[\alpha]_D^{+10.5}$  (*c* 1.00, H<sub>2</sub>O);  $\lambda_{max}$  (pH 6 buffer) 261.5 and 278.5 nm (*s* 20,100; 19,200);  $\nu_{max}$  (Nujol) 1770 cm<sup>-1</sup> ( $\beta$ -lactam);  $\tau$  (D<sub>2</sub>O, 100 MHz) values include 1.03, 1.43, 1.91 (pyridinium protons), 4.12 (dd, 7-H) and 8.50 (s, C(CH<sub>3</sub>)<sub>2</sub>).

## Examples 47—51.

In the manner of Example 46 the acetoxymethyl group of (6R,7R) - 3 - acetoxymethyl - 7 - [2 - (carboxy - R<sup>a</sup> - oxyimino) - 2 - (fur - 2 - yl)acetamido]ceph - 3 - em - 4 - carboxylic acids (*syn* isomers) were displaced by treatment with pyridine or a substituted pyridine in aqueous sodium iodide solution at 80° for 45—60 minutes. The products were purified as the sodium salts by XAD-2 chromatography and their physical properties are summarised in Table 7.

TABLE 7



Ex. No.	R <sup>q</sup>	P	Salt	[α] <sub>D</sub>	λ <sub>max</sub> , nm (pH 6 buffer)	ε	β-lactam ν <sub>max</sub> , cm <sup>-1</sup> (Nujol)	τ values for D <sub>2</sub> O at 100 MHz		
								x	y	R <sup>q</sup>
47	-CH <sub>2</sub> -		monosodium	-	260.5 278	14,500 14,100		-	4.16	5.45
48			monosodium	-	-	-		-	4.11	8.48
49			disodium	-	270.5	19,100		-	4.11	8.48
50			monosodium	-	260.5 280.5	19,100 19,100	-	-	4.16	7.92; 8.30
51			monosodium	+14° (H <sub>2</sub> O)	260 280.5	19,400 18,550	1770	-	4.11	7.58; 8.03



## Example 52.

- (6R,7R) - 7 - [2 - (2 - Carboxyprop - 2 - yloxyimino) - 2 - (fur - 2 - yl) - acetamido] - 3 - pyridaziniummethylceph - 3 - em - 4 - carboxylic acid trifluoroacetate (*syn isomer*)
- (a) A suspension of diphenylmethyl (1S,6R,7R) - 3 - bromomethyl - 7 - [2 - (2 - *t* - butoxycarbonylprop - 2 - yloxyimino) - 2 - (fur - 2 - yl)acetamido]ceph - 3 - em - 4 - carboxylate 1-oxide (*syn isomer*) (1.51 g) in N,N-dimethylformamide (1 ml) was treated with pyridazine (400 mg). The mixture was stirred for 2 hours at 25° to give a clear solution, which was then diluted with ether (50 ml, added slowly with stirring). The resulting precipitate was filtered off, washed with ether and dried to give diphenylmethyl (1S,6R,7R) - 7 - [2 - (2 - *t* - butoxycarbonylprop - 2 - yloxyimino) - 2 - (fur - 2 - yl)acetamido] - 3 - pyridaziniummethylceph - 3 - em - 4 - carboxylate 1-oxide (*syn isomer*) as a pink powder (1.59 g, 94%);  $[\alpha]_D + 13^\circ$  (*c* 1.07, DMSO);  $\lambda_{max}$  (EtOH) 277 nm ( $\epsilon$  21,200);  $\nu_{max}$  (Nujol) 1790  $\text{cm}^{-1}$  ( $\beta$ -lactam);  $\tau$  ( $d_4$ -DMSO) values include 1.21 (d, J 8 Hz, NH), 3.76 (dd, J 4 and 8 Hz, 7-H), 8.51 (s, C(CH<sub>3</sub>)<sub>2</sub>) and 8.61 (s, C(CH<sub>3</sub>)<sub>2</sub>).
- (b) The product of (a) above (1.49 g) in N,N-dimethylformamide (5 ml) at -10° was treated with potassium iodide (1.33 g) and then with acetyl chloride (0.28 ml). The mixture was stirred for 1 hour while the temperature slowly rose to 0°, and was then added dropwise to a stirred solution of sodium metabisulphite (1 g) in water (50 ml). The resulting suspension was stirred for 10 minutes and then the solid material was filtered off, washed with water and dried over phosphorus pentoxide to give a light brown powder (1.28 g). This material, in acetone:ethanol=9:1 (20 ml), was passed down a column of Deacidite FF resin (trifluoroacetate form, 15 cm x 2.5 cm i.d.) which was eluted with the same solvent mixture. Eluant fractions containing ultraviolet light absorbing material were combined and evaporated, and the residue was triturated with ether to give diphenylmethyl (6R,7R) - 7 - [2 - (2 - *t* - butoxycarbonyl - prop - 2 - yloxyimino) - 2 - (fur - 2 - yl)acetamido] - 3 - pyridaziniummethylceph - 3 - em - 4 - carboxylate trifluoroacetate (*syn isomer*), (1.24 g, 82%);  $[\alpha]_D - 20^\circ$  (*c* 0.76, DMSO);  $\lambda_{max}$  (EtOH) 278 nm ( $\epsilon$  18,300);  $\nu_{max}$  (Nujol) 1780  $\text{cm}^{-1}$ ;  $\tau$  ( $d_4$ -DMSO) values include 0.30 (d, J 8 Hz, NH), 3.95 (dd, J 5 and 8 Hz, 7-H), 8.55 (s, C(CH<sub>3</sub>)<sub>2</sub>) and 8.59 (s, C(CH<sub>3</sub>)<sub>2</sub>).
- (c) The product of (b) above (1.13 g), mixed with anisole (1.5 ml), was treated with trifluoroacetic acid (6 ml) at 5° for 5 minutes, and then at 20° for 55 minutes. The solution was evaporated *in vacuo*; the residue was stirred with ethyl acetate, and the evaporation

repeated. The resulting gum was triturated with ether to give the crude product as a pale brown solid, which was filtered off, washed with ether and dried. This was extracted with water (3 x 150 ml); the extracts were filtered, washed with ethyl acetate and then ether, and finally freeze-dried. The combined residues were triturated with ether to give the *title salt* as a white powder (586 mg, 72%);  $[\alpha]_D + 48^\circ$  (*c* 0.98, DMSO);  $\lambda_{max}$  (pH 6 phosphate buffer) 277 nm ( $\epsilon$  18,100);  $\nu_{max}$  (Nujol) 1776  $\text{cm}^{-1}$  ( $\beta$ -lactam);  $\tau$  ( $d_4$ -DMSO) 0.37 (d J 8 Hz, NH), 4.09 (dd, J 5 and 8 Hz, 7-H) and 8.53 (s, C(CH<sub>3</sub>)<sub>2</sub>).

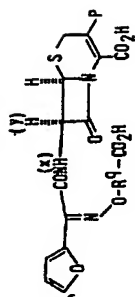
## Examples 53—58.

The trifluoroacetate salts listed in Table 8 were prepared by reacting the 3-bromomethyl ester (see below) with the appropriate tertiary base (or quaternary mercaptan for example 55), reducing the sulphoxide and removing both protecting groups in a similar manner to that described in Example 52. The starting material was prepared as follows:—

A solution of phosphorus pentachloride (5.20 g) in dry dichloromethane (60 ml) at -10° was treated with N,N-dimethylacetamide (12 ml), and then with 2 - (2 - *t* - butoxycarbonylprop - 2 - yloxyimino) - 2 - (fur - 2 - yl)acetic acid (*syn isomer*) (6.43 g) added portionwise. The solution was stirred at -10° for 15 minutes and then ice (14 g) was slowly added and the temperature allowed to rise to 0° over 10 minutes. The organic layer was separated and added dropwise to a suspension of diphenylmethyl (1S,6R,7R) - 7 - amino - 3 - bromomethylceph - 3 - em - 4 - carboxylate 1-oxide hydrobromide (10.62 g) in dichloromethane (80 ml) containing propylene oxide (15 ml) at 0°. The mixture was stirred for 1 hour during which time the temperature rose to 20° and the suspension cleared. The resulting yellow solution was washed with 2.5% aqueous sodium bicarbonate solution (50 ml) and then 2N - hydrochloric acid (>0 ml), whereafter the solution was dried and evaporated to a yellow oil. This material, in ethyl acetate (20 ml), was added dropwise to stirred petrol (b.p. 40—60°) to give a gummy precipitate. The supernatant was decanted off and the gum chromatographed on a column of Kieselgel, which was eluted with dichloromethane containing from 0 to 10% acetone. Eluant fractions containing the main product were combined and evaporated to a foam. Trituration with cyclohexane gave diphenylmethyl (1S,6R,7R) - 3 - bromomethyl - 7 - [2 - (2 - *t* - butoxycarbonylprop - 2 - yloxyimino) - 2 - (fur - 2 - yl) - acetamido]ceph - 3 - em - 4 - carboxylate 1-oxide (*syn isomer*) as a pale yellow microcrystalline powder (13.61 g, 90%);  $[\alpha]_D - 22^\circ$  (*c* 1.0, DMSO);  $\lambda_{max}$  (EtOH) 281 nm ( $\epsilon$  22,200);  $\nu_{max}$  (CHBr<sub>3</sub>)

1800  $\text{cm}^{-1}$  ( $\beta$ -lactam);  $\tau$  ( $d_6$  DMSO) values and 8 Hz, 7-H), 8.51 (s,  $\text{C}(\text{CH}_3)_2$ ) and include 1.26 (d, J 8 Hz, NH), 3.86 (dd, J 4 8.61 (s,  $\text{C}(\text{CH}_3)_2$ ).

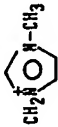
TABLE 8



Ex. No.	$\text{R}^q$	P	Salt	$[\alpha]_D$ (DMSO)	$\lambda_{\text{max}}$ , nm (pH 6 buffer)	$\epsilon$	$\beta$ -lactam $\nu_{\text{max}}$ , $\text{cm}^{-1}$ (Nujol)	$r$ values* for $d_6$ -DMSO at 100 MHz		
								x	y	$\text{R}^q$
53	$>\text{C}(\text{CH}_3)_2$		trifluoroacetate	-57.5°	267	21,600	1775	0.38	4.11	8.55
54	$>\text{C}(\text{CH}_3)_2$		trifluoroacetate	-43.5°	244 277	14,800 18,200	1784	0.4	4.14	8.54
55	$>\text{C}(\text{CH}_3)_2$		trifluoroacetate	-14°	277	21,500	1782	0.40	4.14	8.53
56	$>\text{C}(\text{CH}_3)_2$		trifluoroacetate	-58°	267	22,200	1780	0.29	4.05	8.55
57	$\cdot\text{C}(\text{CH}_3)_2$		trifluoroacetate	-79°	225.5 271	16,100 18,400	1778	0.38	4.12	8.50

\*Values for the trifluoroacetate salt

TABLE 8 (Continued)

Ex. No.	R <sup>q</sup>	P	Salt	[α] <sub>D</sub> (DMSO)	λ <sub>max</sub> , nm (pH 6 buffer)	ε	β-lactam ν <sub>max</sub> , cm <sup>-1</sup> (Nujol)	r values* for d <sub>6</sub> -DMSO at 100 MHz		
								x	y	R <sup>q</sup>
58	C(CH <sub>3</sub> ) <sub>2</sub>		trifluoroacetate	-32°	274	18,100	1773	0.40	4.11	8.53

\*Values for the trifluoroacetate salt

## Example 59.

(6R,7R) - 3 - (Benzotriazol - 1 - ylmethyl) -  
 7 - [2 - (2 - carboxyprop - 2 - yloxy-  
 imino) - 2 - (fur - 2 - yl)acetamido]ceph-  
 3 - em - 4 - carboxylic acid (*syn isomer*)  
 Diphenylmethyl (1S,6R,7R) - 3 - bromo-  
 methyl - 7 - [2 - (2 - *t* - butoxycarbonylprop -  
 2 - yloxyimino) - 2 - (fur - 2 - yl)acetamido] -  
 ceph - 3 - em - 4 - carboxylate 1-oxide (*syn*  
 isomer) (1.51 g) in N,N-dimethylformamide  
 (3 ml) was stirred with benzotriazole (480  
 mg) for 4 days. The solution was diluted  
 with dichloromethane and then washed twice  
 with 2N-hydrochloric acid; the solution was  
 then dried and evaporated, and the main pro-  
 duct was isolated from the residue by column  
 chromatography on Kieselgel, with chloro-  
 form containing 0 to 10% v/v acetone for  
 elution. This material (700 mg) in N,N -  
 dimethylformamide (2 ml) with potassium  
 iodide (665 mg) at -10° was treated with  
 acetyl chloride (0.14 ml). The suspension was  
 stirred for 1.25 hours and allowed to warm  
 slowly to 0°, and was then added dropwise

to water (40 ml) containing sodium meta-  
 bisulphite (0.5 g). The precipitate was filtered  
 off, washed with water, dried, and purified  
 by chromatography on Kieselgel, eluting with  
 dichloromethane containing from 0 to 3%  
 v/v acetone.

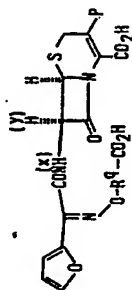
The diester so obtained (520 mg), to-  
 gether with anisole (0.5 ml), was treated  
 with trifluoroacetic acid (2 ml) at 25° for 1  
 hour. The solution was then added dropwise  
 with stirring to saturated aqueous sodium  
 bicarbonate (50 ml) and ice (25 g). The  
 mixture was stirred, whereafter ethyl acetate  
 was added. The aqueous layer was separated  
 and acidified under ethyl acetate to pH 2.  
 The organic layer was separated, and the  
 aqueous layer extracted with more ethyl ac-  
 etate. The combined extracts were dried and  
 concentrated to an oil, which was added drop-  
 wise to stirred petrol (b.p. 40-60°). The  
 white precipitate was filtered off, washed with  
 petrol and dried to give the *title dicarboxylic*  
*acid* as a white powder (350 mg, 31%);  
 [α]<sub>D</sub>+37° (c 1.02, DMSO); λ<sub>max</sub> (pH 6

phosphate buffer) 269 nm ( $\epsilon$  23,600);  $\nu_{\max}$  (Nujol) 1780  $\text{cm}^{-1}$  ( $\beta$ -lactam);  $\tau$  (d<sub>g</sub>-DMSO) values include 0.40 (d, J 8 Hz, NH), 4.11 (dd, J 5 and 8 Hz, 7-H) and 8.53 (s, C(CH<sub>3</sub>)<sub>2</sub>).

### Example 60.

The compound listed in Table 9 was prepared from the appropriate nucleophile using the method of Example 59.

TABLE 9



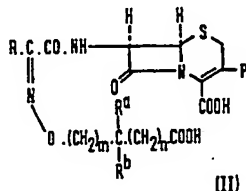
Ex. No.	R <sup>2</sup>	P	Salt	[α] <sub>D</sub> (DMSO)	λ <sub>max</sub> , nm (pH 6 buffer)	ε	β-lactam ν <sub>max</sub> , cm <sup>-1</sup> (Nujol)	r values for d <sub>6</sub> -DMSO at 100 MHz		
								x	y	R <sup>q</sup>
60	$>\text{C}(\text{CH}_3)_2$		--	+2°	272	18,100	1780	0.41	4.11	8.52

### Example 61.

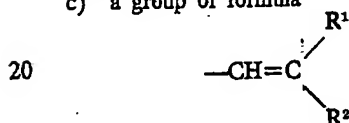
- (1*R*,6*R*,7*R*) - 3 - Acetoxymethyl - 7 - [2 - (2 - carboxyprop - 2 - yloximino) - 2 - (fur - 2 - yl)acetamido]ceph - 3 - em - 4 - carboxylic acid 1-oxide (*syn isomer*)
- 15 (a) A solution of (6*R*,7*R*) - 3 - acetoxymethyl - 7 - [2 - (2 - carboxyprop - 2 - yloximino) - 2 - (fur - 2 - yl)acetamido] - cep - 3 - em - 4 - carboxylic acid, di - t - butyl ester (*syn isomer*), (1.21 g) in pyridine (25 ml) and water (1 ml) at -45° was treated with *t*-butyl hypochlorite (0.3 ml) with vigorous stirring. After 2 minutes 2*N*-sulphurous acid (1 ml) was added to the solution and the mixture was immediately poured into aqueous phosphoric acid (100 ml, 20% v/v). The aqueous solution was extracted with ethyl acetate and the organic extracts were washed with 0.5*N*-hydrochloric acid (50 ml), aqueous sodium bicarbonate solution (50 ml) and water, then dried and concentrated *in vacuo*. The crude product was chromatographed on silica gel preparative plates, using ethyl acetate:petroleum ether (b.p. 60-80°) (4:1) as eluant. The slower running band was extracted with ethyl acetate
- 25
- 30
- 35

(wherein R is thienyl or furyl; R<sup>a</sup> and R<sup>b</sup>, which may be the same or different, are each selected from hydrogen, C<sub>1-4</sub> alkyl, C<sub>2-4</sub> alkenyl, C<sub>2-7</sub> cycloalkyl, phenyl, naphthyl, thienyl, furyl, carboxy, C<sub>2-5</sub> alkoxy carbonyl, 105

- and cyano, or  $R^a$  and  $R^b$  together with the carbon atom to which they are attached form a  $C_{2-7}$  cycloalkylidene or cycloalkenylidene group; and  $m$  and  $n$  are each 0 or 1 such that the sum of  $m$  and  $n$  is 0 or 1), the compounds being *syn* isomers or existing as mixtures of *syn* and *anti* isomers containing at least 90% of the *syn* isomer.
2. A compound as claimed in claim 1 which is a *syn* isomer essentially free from the *anti* isomer.
3. Compounds as claimed in claim 1 or claim 2 having the general formula



- 15 [where  $R$ ,  $R^a$ ,  $R^b$ ,  $m$  and  $n$  are as defined in claim 1 and  $P$  is selected from:—
- hydrogen,
  - halogen,
  - a group of formula



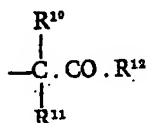
wherein  $R^1$  and  $R^2$ , which may be the same or different, are each selected from hydrogen, carboxy, cyano,  $C_{2-7}$  alkoxy carbonyl,  $C_{1-6}$  alkyl,  $C_{6-7}$  cycloalkyl, phenyl  $C_{1-4}$  alkyl and  $C_{6-10}$  mono- or bicyclic carbocyclic aryl, and

25 d) a group of formula



wherein  $Y$  is selected from:—

- 30 d) (i) the residue of a nitrogen nucleophile which is a tri( $C_{1-6}$  alkyl) amine or a heterocyclic tertiary amine,
- d) (ii) azido,
- d) (iii) amino,
- d) (iv) acylamido,
- 35 d) (v) a derivative obtained by reacting a compound in which  $Y$  is a azido with an acetylenic, ethylenic or cyano dipolarophile,
- d) (vi) a group of formula

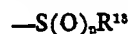


- 40 wherein  $R^{10}$  and  $R^{11}$ , which may be the same or different, are each selected from hydrogen; cyano; lower alkyl; phenyl; phenyl substituted by one or more of halo, lower alkyl, lower

alkoxy, nitro, amino or lower alkylamino; carboxy; lower alkoxy carbonyl; mono- or diaryl lower alkoxy carbonyl; lower alkyl carbonyl; aryl lower alkyl; and  $C_6$  and  $C_6$  cycloalkyl; and  $R^{12}$  is selected from hydrogen; lower alkyl; phenyl; phenyl substituted by one or more of halo, lower alkyl, lower alkoxy, nitro, amino or lower alkylamino; aryl lower alkyl; and  $C_6$  and  $C_6$  cycloalkyl;

d) (vii) the residue of a sulphur nucleophile which is a thiourea, dithiocarbamate, thioamide, thiosulphate, thioacid or dithioacid,

d) (viii) a group of formula



wherein  $R^{13}$  is a lower alkyl, lower cycloalkyl, phenyl lower alkyl,  $C_{6-12}$  mono- or bicyclic carbocyclic aryl or heterocyclic group and  $n$  is 0, 1 or 2,

d) (ix) a group of formula



wherein  $R^{15}$  is hydrogen, lower alkyl, lower alkenyl, lower alkynyl, lower cycloalkyl, lower cycloalkyl lower alkyl, aryl, aryl lower alkyl, heterocyclic, heterocyclic lower alkyl, or any of the preceding groups substituted by one or more of lower alkoxy, lower alkylthio, halogen, lower alkyl, nitro, hydroxy, acyloxy, carboxy, lower alkoxy carbonyl, lower alkyl carbonyl, lower alkylsulphonyl, lower alkoxy sulphonyl, amino, lower alkylamino and acylamino,

d) (x) a group of formula



wherein  $R^{16}$  is selected from  $C_{1-7}$  alkyl, which may be interrupted by an oxygen or sulphur atom or by an imino group or substituted by cyano, carboxy, lower alkoxy carbonyl, hydroxy, carboxy carbonyl, halogen or amino;  $C_{2-7}$  alkenyl, which may be interrupted by an oxygen or sulphur atom or by an imino group; lower cycloalkyl; carbocyclic or heterocyclic aryl, which may be substituted by hydroxy, halo, nitro, amino, lower alkyl or lower alkylthio; lower cycloalkyl  $C_{1-7}$  alkyl; and carbocyclic or heterocyclic aryl  $C_{1-4}$  alkyl and

d) (xi) a group of formula



wherein  $R^{17}$  is hydrogen or a group as defined above for  $R^{16}$  and  $A$  is  $>O$ ,  $>S$  or  $>NH$ ] and non-toxic derivatives thereof.

4. Compounds as claimed in claim 3 wherein  $P$  is a group of formula



in which  $Y$  is the residue of a nitrogen nucleophile

phile comprising pyridine, pyrimidine, pyridazine, pyrazine, pyrazole, imidazole, triazole, thiazole, purine, benzotriazole or any of these compounds substituted by one or more lower alkyl, C<sub>6-12</sub> mono- or bicyclic carbocyclic aryl, phenyl lower alkyl, lower alkoxyethyl, acyloxymethyl, formyl, acyloxy, carboxy, esterified carboxy, carboxy lower alkyl, sulpho, lower alkoxy, phenoxy, phenyl lower alkoxy, lower alkylthio, phenylthio, phenyl lower alkylthio, cyano, hydroxy, carbamoyl, N-mono(lower alkyl carbamoyl, N,N-di(lower alkyl) carbamoyl, N-(hydroxy lower alkyl) carbamoyl or carbamoyl lower alkyl groups.

- 15 5. Compounds as claimed in claim 3 wherein P is a group of formula



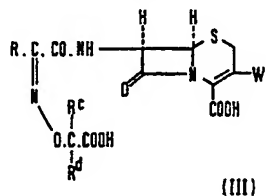
in which Y is a group



- 20 wherein R<sup>14</sup> is a diazoly, triazolyl, tetrazolyl, thiazolyl, thiadiazolyl, thiatriazolyl, oxazolyl, oxadiazolyl, pyridyl, pyrimidyl, benzimidazolyl, benzoxazolyl, benzothiazolyl, triazolopyridyl or purinyl group.

- 25 6. Compounds as claimed in claim 3 wherein P is an acetoxymethyl or carbamoyloxymethyl group.

7. Compounds as claimed in claim 1 or claim 2 having the general formula



[wherein R is as defined in claim 1; R<sup>c</sup> represents methyl, ethyl, propyl, allyl or phenyl and R<sup>d</sup> represents hydrogen, carboxy or a group as defined for R<sup>c</sup>, or R<sup>c</sup> and R<sup>d</sup> together with the carbon atom to which they are attached form a cyclobutylidene, cyclopentylidene or cyclohexylidene group; and W is selected from:—

- 35 i) hydrogen,  
40 ii) acetoxymethyl,  
iii) benzoyloxymethyl,  
iv) carbamoyloxymethyl,  
v) N-methylcarbamoyloxymethyl,  
vi) a group of formula

- 45  $-\text{CH}=\text{CHR}^*$

wherein R<sup>\*</sup> represents cyano, carboxy or C<sub>2-6</sub> alkoxy-carbonyl,  
vii) a group of formula



wherein G is the residue of a nitrogen nucleophile selected from compounds of the formula



(wherein R' is hydrogen, carbamoyl, carboxymethyl or sulpho) and pyridazine,  
viii) azidomethyl, and  
ix) a group of formula



wherein R<sup>\*</sup> is a pyridyl, diazoly, triazolyl, tetrazolyl, thiazolyl, thiadiazolyl or oxadiazolyl group or a lower alkyl- or phenyl-substituted analogue of such a group] and non-toxic derivatives thereof.

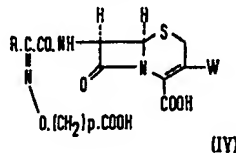
8. Compounds as claimed in claim 7 wherein W is a group of formula



in which R<sup>\*</sup> is N-methylpyrid-2-yl, 1-methyltetrazol-5-yl or 5-methyl-1,3,4-thiadiazol-2-yl.

9. The compounds of claims 7 and 8 wherein R<sup>d</sup> is other than hydrogen.

10. Compounds as claimed in claim 1 or claim 2 having the general formula



[wherein R is as defined in claim 1; W is as defined in claim 7; and p is 1 or 2] and non-toxic derivatives thereof.

11. Compounds as claimed in claim 10 wherein W is a group as defined in claim 8.

12. (6R,7R) - 7 - [2 - (2 - Carboxyprop-2-yloxyimino) - 2 - (fur-2-yl) acetamido] - 3 - pyridiniummethylceph - 3 - em - 4 - carboxylic acid (syn isomer).

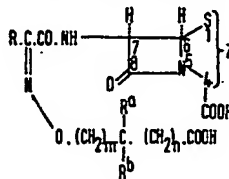
13. (6R,7R) - 7 - [2 - (2 - Carboxyprop-2-yloxyimino) - 2 - (fur-2-yl) acetamido] - 3 - (5-methyl-1,3,4-thiadiazol-2-ylthiomethyl) cep - 3 - em - 4 - carboxylic acid (syn isomer).

14. (6R,7R) - 7 - [2 - (2 - Carboxyprop-2-yloxyimino) - 2 - (fur-2-yl) acetamido] - 3 - (trans-2-methoxycarbonylvinyl) cep - 3 - em - 4 - carboxylic acid (syn isomer).

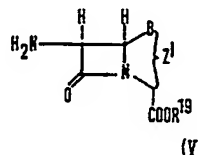
15. (6R,7R) - 7 - [2 - (2 - Carboxyprop-2-yloxyimino) - 2 - (fur-2-yl) acetamido] - 3 - pyridaziniummethylceph - 3 - em - 4 - carboxylic acid (syn isomer).

16. (6R,7R) - 7 - [2 - (2 - Carboxyprop-2-yloxyimino) - 2 - (fur-2-yl) acetamido] cep - 3 - em - 4 - carboxylic acid (syn isomer).

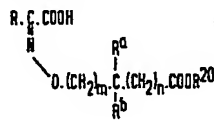
17. (6R,7R) - 3 - acetoxymethyl - 7 - [2 - (1 - carboxycyclopent - 1 - yloxyimino) - 2 - (fur - 2 - yl)acetamido]ceph - 3 - em - 4 - carboxylic acid (*syn* isomer). 65
- 5 18. (6R,7R) - 7 - (1 - carboxycyclopent - 1 - yloxyimino) - 2 - (fur - 2 - yl)acetamido] - 3 - pyridiniummethylceph - 3 - em - 4 - carboxylic acid (*syn* isomer). 70
- 10 19. (6R,7R) - 7 - [2 - (1 - carboxycyclopent - 1 - yloxyimino) - 2 - (fur - 2 - yl)acetamido] - 3 - (trans - 2 - carboxyvinyl)ceph - 3 - em - 4 - carboxylic acid (*syn* isomer).
- 15 20. (6R,7R) - 7 - [2 - (1 - Carboxycyclopent - 1 - yloxyimino) - 2 - (fur - 2 - yl)acetamido] - 3 - (1 - methyltetrazol - 5 - ylthiomethyl)ceph - 3 - em - 4 - carboxylic acid (*syn* isomer).
- 20 21. (6R,7R) - 7 - [2 - (1 - Carboxycyclopent - 1 - yloxyimino) - 2 - (fur - 2 - yl)acetamido]ceph - 3 - em - 4 - carboxylic acid (*syn* isomer).
- 25 22. (6R,7R) - 3 - Acetoxymethyl - 7 - [2 - (1 - carboxybut - 3 - enyloxyimino) - 2 - (fur - 2 - yl)acetamido]ceph - 3 - em - 4 - carboxylic acid (*syn* isomer).
- 30 23. (6R,7R) - 3 - Acetoxymethyl - 7 - [2 - (1 - carboxycyclobut - 1 - yloxyimino) - 2 - (fur - 2 - yl)acetamido]ceph - 3 - em - 4 - carboxylic acid (*syn* isomer).
- 35 24. (6R,7R) - 7 - [2 - (1 - Carboxycyclobut - 1 - yloxyimino) - 2 - (fur - 2 - yl)acetamido] - 3 - pyridiniummethylceph - 3 - em - 4 - carboxylic acid (*syn* isomer).
- 40 25. (6R,7R) - 7 - [2 - (1 - Carboxycyclobut - 1 - yloxyimino) - 2 - (fur - 2 - yl)acetamido] - 3 - (1 - methyltetrazol - 5 - ylthiomethyl)ceph - 3 - em - 4 - carboxylic acid (*syn* isomer).
- 45 26. (6R,7R) - 3 - Acetoxymethyl - 7 - [2 - (1 - carboxypropoxyimino - 2 - (fur - 2 - yl)acetamido]ceph - 3 - em - 4 - carboxylic acid (*syn* isomer).
- 50 27. (6R,7R) - 3 - Acetoxymethyl - 7 - [2 - (3 - carboxypent - 3 - yloxyimino) - 2 - (fur - 2 - yl)acetamido]ceph - 3 - em - 4 - carboxylic acid (*syn* isomer).
- 55 28. (6R,7R) - 3 - Acetoxymethyl - 7 - [2 - (2 - carboxyprop - 2 - yloxyimino) - 2 - (thien - 2 - yl)acetamido]ceph - 3 - em - 4 - carboxylic acid (*syn* isomer).
- 60 29. (6R,7R) - 3 - Acetoxymethyl - 7 - [2 - carboxymethoxyimino - 2 - (fur - 2 - yl)acetamido]ceph - 3 - em - 4 - carboxylic acid (*syn* isomer).
30. (6R,7R) - 3 - Azidomethyl - 7 - [2 - carboxymethoxyimino - 2 - (fur - 2 - yl)acetamido]ceph - 3 - em - 4 - carboxylic acid (*syn* isomer).
31. (6R,7R) - 7 - [2 - Carboxymethoxyimino - 2 - (fur - 2 - yl)acetamido] - 3 - (1 - methyltetrazol - 5 - ylthiomethyl)ceph - 3 - em - 4 - carboxylic acid (*syn* isomer).
32. (6R,7R) - 7 - [2 - Carboxymethoxyimino - 2 - (fur - 2 - yl)acetamido]ceph - 3 - em - 4 - carboxylic acid (*syn* isomer).
33. (6R,7R) - 7 - [2 - Carboxyprop - 2 - yloxyimino - 2 - (fur - 2 - yl) - acetamido]ceph - 3 - em - 4 - carboxylic acid (*syn* isomer).
34. The sodium and potassium salts of the acids claimed in any of the preceding claims.
35. A process for the preparation of an antibiotic compound of general formula



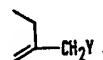
(wherein R, R<sup>a</sup>, R<sup>b</sup>, m and n are as defined in claim 1) and Z is a group in which 2 carbon atoms link the nuclear sulphur atom and the 4-position carbon atom so that the compound possesses Δ<sup>3</sup> unsaturation) or a non-toxic derivative thereof, said compound being a *syn* isomer or existing as a mixture of *syn* and *anti* isomers containing at least 90% of the *syn* isomer, which comprises either (A) condensing a compound of the formula



(wherein B is >S or >S→O; R<sup>19</sup> represents hydrogen or a carboxyl blocking group; and Z' is a group in which 2 carbon atoms link the nuclear sulphur atom and the 4-position carbon atom so that the compound possesses Δ<sup>2</sup> or Δ<sup>3</sup> unsaturation) or an acid addition salt or an N-silyl derivative thereof with an acylating agent corresponding to an acid of

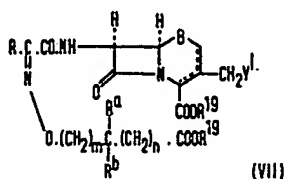


(wherein R, R<sup>a</sup>, R<sup>b</sup>, m and n are as hereinbefore defined and R<sup>20</sup> is a carboxyl blocking group); or (B), where Z in formula I is the group



(where Y is the residue of a nucleophile or a derivative of the residue of a nucleophile) reacting a compound of the formula





(wherein B, R, R<sup>a</sup>, R<sup>b</sup>, m and n are as hereinbefore defined; each R<sup>19</sup> may independently represent hydrogen or a carboxyl blocking group; Y' is an atom or group which is replaceable by the residue of a nucleophile; and the dotted line bridging the 2-, 3- and 4-positions indicates that the compound is a ceph - 2 - em or ceph - 3 - em compound) with a nucleophile; whereafter, if necessary and/or desired in each instance, any of the following reactions (C), in any appropriate sequence, are carried out:—

- i) conversion of a Δ<sup>2</sup> isomer into the desired Δ<sup>3</sup> isomer,
  - ii) reduction of a compound wherein B is >S→O to form a compound wherein B is >S,
  - iii) reduction of a 3-azidomethyl compound to form a 3-aminomethyl compound,
  - iv) acylation of a 3-aminomethyl compound to form a 3-acylaminomethyl compound,
  - v) reaction of a 3-azidomethyl compound with a dipolarophile to form a compound having a polyazole ring linked to the 3-position carbon atom through a methylene group,
  - vi) deacylation of a 3-acyloxymethyl compound to form a 3-hydroxymethyl compound,
  - vii) acylation of a 3-hydroxymethyl compound to form a 3-acyloxymethyl compound,
  - viii) carbamoylation of a 3-hydroxymethyl compound to form an unsubstituted or substituted 3-carbamoyloxymethyl compound, and
  - ix) removal of carboxyl blocking groups; and finally (D) recovering the desired compound of formula I or a non-toxic derivative thereof, if necessary after separation of isomers.
36. A process as claimed in claim 35 wherein a compound (V) or an acid addition-

salt or N-silyl derivative thereof is condensed with an acid halide corresponding to the acid (VI).

37. A process as claimed in claim 36 wherein the condensation is effected in the presence of an acid binding agent comprising a tertiary amine, an inorganic base or an oxirane.

38. A process as claimed in claim 35 wherein a compound (V) or an acid addition salt or N-silyl derivative thereof is condensed with an acid (VI) in the presence of a condensation agent comprising a carbodiimide, carbonyldiimidazole or an isozazolinium salt.

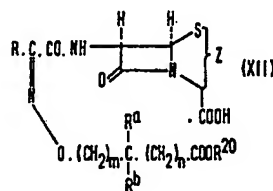
39. A process as claimed in claim 35 substantially as herein described.

40. A process for the preparation of antibiotic compounds as defined in claim 1 substantially as herein described with particular reference to any one of the Examples.

41. Antibiotic compounds as defined in claim 1 whenever prepared by a process as claimed in any of claims 35 to 40.

42. A pharmaceutical composition comprising an antibiotic compound as claimed in any of claims 1 to 34 or 41 in a form adapted for use in human or veterinary medicine.

43. Compounds of general formula



(wherein R, R<sup>a</sup>, R<sup>b</sup>, R<sup>20</sup>, Z, m and n are as defined in claim 35).

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